THE BANTING MEMORIAL LECTURE 1956

Recent Advances in Insulin Research

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INTRODUCTION

Dr. Ricketts, Members of the Association and Guests: I am indeed highly honored that this Society has selected me, one who long since abandoned the bedside for the laboratory, to give the Banting Lecture. I am happy to join with this Association to pay tribute to a great physician whose discovery of insulin has done so much to diminish suffering in man. Outstanding discoveries in the field of medical therapy are rare. We count surgical asepsis, anesthetics, and antibiotics among the important ones. The imperishable studies of Banting and Best added insulin to these. Its discovery generated problems in many areas of medicine and these have aroused the imagination and stimulated the activities of scientists all over the world. Driven by insatiable intellectual curiosity, they have labored indefatigably to search out the mode of action of insulin upon mammalian metabolism. Although obscurity still darkens the field, these researches reveal a pattern which begins to have meaning. I have undertaken the task in this hour to describe this pattern as I see it.

TRANSPORT HYPOTHESIS

The history of diabetes is replete with attempts to explain why the early steps in the metabolism of glucose are impaired in the disease. Many of these invoked what was called "activation" of glucose, supposing mechanisms of one sort or another which made glucose more easily metabolizable. These now have only historical interest. A possible role of the cell membrane in such theories received little or no attention although it was well known that cellular membranes had specific properties which enabled them to exclude certain substances from entrance and permitted others to sustain high concentration gradients across cell boundaries. Hoeber, in 1927, appears to be the first to propose a definite "membrane theory of diabetes." He was led to formulate this hypothesis from his studies on the permeability of red blood cells of various animal species. He suggested the possibility that certain pathological relationships in cellular metabolism could be brought about by disturbances in the normal permeability of cells. "One thinks," he said, "that an abnormal constitution of the cell membrane (perhaps of the liver cell) does not allow the simple sugars to reach their normal locus of breakdown. If one considers the above possibility it is possible to substitute for the present theory of diabetes, which is based upon concepts of abnormal enzymatic activities, another viewpoint: the membrane theory of diabetes."[1]

These speculations of Hoeber bore fruit some quarter of a century later. Two investigators, Levine[2] of Chicago and Ross[3, 4, 5] of the London Ophthalmological Institute, were stimulated to study the possible role of permeability factors in diabetes. They approached the subject from two different points of view.

Levine was influenced by early experiments with Soskin[6] from which they concluded that elevation of the blood sugar in the diabetic state in part compensates for insulin lack and restores glucose oxidation in peripheral tissues. It was natural to suppose that permeability factors were involved. To test the basic hypothesis that insulin accelerated the rate of entry of glucose into the tissues, Levine and his co-workers[7] devised the experiment illustrated in figure 1.

Levine selected galactose because it is essentially inert in the peripheral tissues. Eviscerated animals were used to eliminate the action of the liver, kidney, and intestines which are known to metabolize galactose. Following intravenous injection into the preparation, the blood galactose levels were followed for a period of two to six hours when constant values were reached. From these the volume of distribution of galactose was calculated. The upper curve shows that without insulin, the volume of distribution of galactose was approximately 45 per cent of the body weight. When insulin was

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injected prior to the injection of galactose, the volume of distribution, shown in the lower curve, was significantly increased and was of the order of 70 per cent of body weight, essentially that of body water. In similar experiments other sugars were studied. These were divided by Levine into two groups: (1) those nonresponsive to insulin in that their volume of distribution is uninfluenced by the simultaneous administration of the hormone and (2) sugars which are responsive to insulin, the volume of distribution being increased. In addition to galactose, l-arabinose and d-xylose were found to be insulin responsive. These three sugars were all characterized by having the same configuration in carbons 1, 2 and 3. From these data, Levine concluded that the entrance of sugar into muscle "is governed by a transfer system which is specifically adapted with respect to chemical structure." Since glucose resembles the insulin responsive sugars structurally with respect to the configuration of carbons 1, 2 and 3, the authors concluded that glucose is also insulin responsive.

Ross[3, 4, 5] at the London Ophthalmological Institute was influenced to study the subject by different considerations. He was interested in determining the factors which govern the passage of substances from the blood across the ciliary body into the aqueous humour of the eye. This system is convenient for permeability studies, since it is possible to vary the blood concentration at will and obtain samples of aqueous humour at any given time. Ross studied the rate of penetration into the aqueous humour of a number of substances and looked for correlation of these rates with a variety of chemical or physical properties of the solutes. Significant correlation was found only with the relative water-lipid solubility. These data are shown in figure 2.

Along the ordinates are shown the rates of entrance of the solute into the aqueous humour expressed as a permeability constant K. Along the abscissa are expressed the ratio of the solubility of the solute in ether to its solubility in water. This ratio is thus a measure of the relative solubility of the solute in a lipid as compared to its solubility in water. A value to the right indicates that the substance is highly lipid soluble. Contrariwise, a value to the left indicates high water solubility. The more readily lipid-soluble solutes, such as ethyl alcohol shown in the extreme right hand upper corner, have the largest permeability constants. In contrast, the more water soluble solutes had low permeability constants. Ross concluded that these relationships are in accord with current concepts of cellular membrane structure which, according to Overton, are of lipid character. Transport into the cell is thus a function

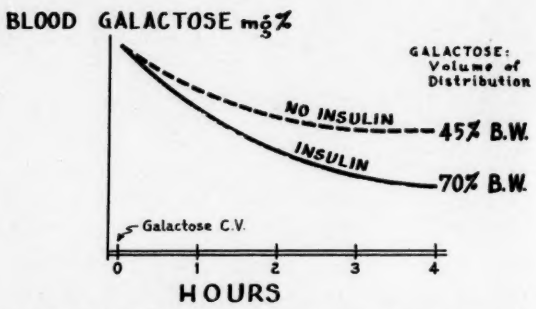

FIG. 1. Effect of insulin on glucose transport (eviscerate-nephrectomized dog). Data of Levine et al., 1950.

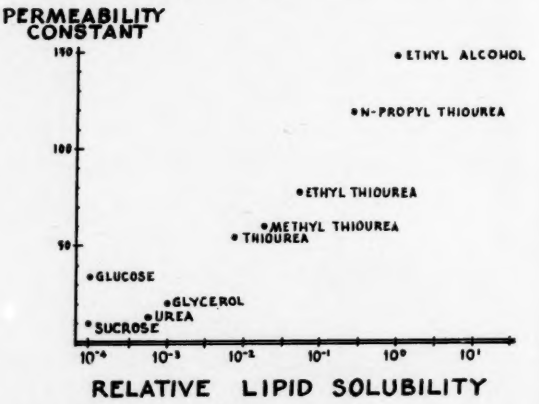

FIG. 2. Relation between transport across blood-aqueous barrier of the eye and the blood lipid solubility of solutes. Data of Ross, 1951.

of the solubility of the solute in the lipid membrane. Ross noted that glucose (at the lower left corner) is out of line. Its permeability constant of thirty-five is four times that of sucrose which had the same relative water-lipid solubility. Ross surmised that some factor accelerates the rate of permeability of glucose through the ciliary body and it was natural to suppose that insulin was the factor. He, therefore, determined permeability rates across the ciliary body of the rabbit eye in the fasting state, in the diabetic state, and in the diabetic state after insulin.

Figure 3 shows some representative data of Ross. In the alloxanized diabetic rabbit with hyperglycemia, the permeability constant was approximately half of the mean value observed in normal rabbits. Prior treatment of the animal with insulin restored the permeability constant to normal values. These effects were attributed by Ross to changes of permeability of the ciliary body to glucose brought about by insulin. Ross noted that, in addition to glucose, other sugars were characterized

by response to insulin to accelerate transport into the aqueous humour. Among these were d-galactose, d-xylose, and d-arabinose. As we have seen, Levine showed by his totally different method that insulin influenced the transport of these sugars across cell boundaries.

Park and his co-workers,[8, 9] in a series of brilliant experiments, were the first to obtain direct evidence that the transport of glucose across cell membranes was accelerated by insulin. Using isotopic glucose with the rat diaphragm, the heart, or the skeletal muscle in vitro, they developed methods for the determination of the effect of insulin upon intracellular free glucose. These experiments gave evidence bearing upon a long-standing problem. The problem is to determine whether insulin acts upon an intracellular enzyme system to accelerate the hexokinase reaction, or upon a cellular membrane system to accelerate transport. Figure 4 makes Park's reasoning clear.

The figure shows schematically a cell membrane separating the medium at the left from the enzyme system situated intracellularly. There are two possible actions of insulin. Case I to the left assumes that insulin accelerates the hexokinase reaction occurring within the cell. Case II assumes that insulin accelerates the transport of glucose from the medium through the membrane into the interior of the cell. In the first case, acceleration of the hexokinase reaction will, compared to controls, decrease the concentration of the intracellular free glucose, i.e., glucose existing within the cell in the non-phosphorylated state. In Case II the opposite occurs: Insulin increases transport of glucose from the medium into the interior of the cell and, therefore, intracellular free glucose is increased. Park and his co-workers reported a large number of experiments which were uniformly consistent. I shall discuss one representative experiment shown in figure 5.

Paired rat diaphragms were equilibrated at 37° respectively without and with insulin in media containing 2,000 mg. per cent glucose. A series of such pairs equilibrated for varying periods of time and then analyzed for free intracellular isotopic glucose in the diaphragm permitted construction of the curves shown in the figure. As the data show, insulin significantly accelerates the transport of glucose across the cell membrane so that the concentration of free glucose within the diaphragm shown in the upper curve is increased above that of the control. From the total evidence obtained by Park and his co-workers, they concluded "that an action of insulin on glucose uptake is to accelerate a step concerned with the transport of glucose into the tissues. This step antecedes and is distinct from glucose

	$1000\ k_{in}$
Normal	199 ± 36
Alloxanized (Blood glucose 400-500 mg %)	102 ± 10
Decrease	97 ± 38
	t = 2.5

FIG. 3. Transfer of glucose across blood-aqueous barrier in rabbit eye. Data of Ross, 1952.

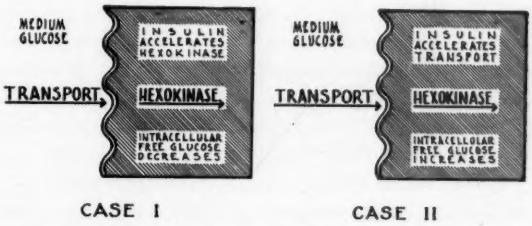

FIG. 4. Differentiation of two theories of insulin action.

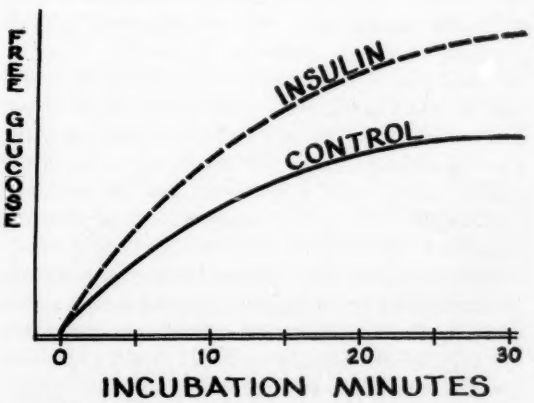

FIG. 5. Effect of insulin on intracellular free glucose in rat diaphragm. Temperature equals 37 degrees C; glucose equals 2,000 mg. per cent. Data of Park et al., 1956.

phosphorylation by the hexokinase reaction."

These conclusions on the effect of insulin on glucose transport in the periphery, coming from three different laboratories, have been supported by other authors. In particular, the experiments of Wick are noteworthy. In the main, his work is in conformity with the reported results in the literature. In addition, he also demonstrated that mannose and glucosamine were insulin responsive. He showed further that insulin responsive sugars competed with each other when both were simultaneously injected into the experimental animal.

Wick demonstrated that analogues of glucose such as 2-oxyglucose are not readily metabolized by tissues and when used experimentally may be manipulated to yield important information about insulin action.

VARIATION OF DIFFERENT TISSUES TO POSSIBLE ACTION OF INSULIN ON GLUCOSE TRANSPORT

The transport hypothesis of insulin action certainly appears to be in the ascendancy at least so far as muscle is concerned. But this conclusion need not be generalized to include all other types of tissue. In fact, there is good evidence to indicate the contrary. For example, the absorption of glucose by the intestines clearly involves passage through cells. But, so far as I am aware, there is no evidence to indicate that in the diabetic animal there is any impairment of glucose absorption. Hence we may conclude that insulin does not influence glucose transport in these cells. The same conclusion may be drawn with respect to kidney cells. The glucose of the glomerular fluid is completely reabsorbed by the tubular cells up to a concentration level of approximately 150-160 mg. per cent. Reabsorption of the glomerular glucose again requires passage through cell membranes and cells. So far as we know the ability of the renal cells of the diabetic is uninfluenced by insulin lack inasmuch as the renal threshold for sugar is not changed in the diabetic state. Glucose is excreted in the urine when blood sugars rise above this value in the normal as well as in the diabetic. But this is due to the limitation of the reabsorptive ability of the cells rather than any lowering of renal threshold.

Another type of tissue, namely brain, appears to have its permeability or transport ability completely unaffected by insulin. This conclusion is based upon the following experimental observations: (1) Brain metabolism appears to be completely unaffected in the diabetic state; (2) no effects of insulin have ever been demonstrated upon any aspect of brain metabolism either in vivo or in vitro; (3) experiments from our laboratory show that isotopic insulin injected intravenously into the intact animal is completely excluded from the brain; (4) and lastly, Park has shown, using isotopic galactose, that in contrast to muscle, insulin does not increase the free galactose concentration of the brain in the experimental animal. In other words, it appears reasonable to assume that the brain has a type of metabolism which does not require insulin.

So far as the liver is concerned, the question of changes of permeability of liver cells to glucose or other metabolites brought about by insulin remains an open question. On the contrary, there is indirect evidence that transport is not involved, viz.: (1) the slowness of recovery to normal of metabolic processes in the diabetic liver following insulin treatment in the intact animal; (2) the complete failure to demonstrate any effect of insulin in vitro upon any metabolic process occurring in liver slices from diabetic animals.

Interesting evidence for this variation of the responsiveness of transport systems of tissues to insulin is shown by experiments in our laboratory reported by Shaw. A small fraction of the total evidence is shown in figure 6. Shaw[10] showed that by selecting appropriate conditions it was possible to demonstrate in the rat diaphragm, coexisting and identical enzyme systems which differ, however, in one respect, namely, their responsiveness to insulin. In the first case, an enzyme system indubitably of the Embden-Meyerhof type was responsive to the presence of insulin in the medium. Accordingly, compared to controls, there was an extra uptake of glucose, an extra production of glucose-6-phosphate, and of glycogen. In the second case, the enzyme system also brought about uptake of glucose from medium, forming lactic acid through the Embden-Meyerhof intermediaries, rather than glycogen as in the first case. But in contrast to the first system, the second system is completely insulin nonresponsive. The data in the figure show these differences of behavior: insulin responsive glycogen forming system on the left; insulin nonresponsiveness lactic acid forming system on the right. This peculiar dichotomy of response in the same tissue is a striking illustration of the variation of tissues to this particular modality of insulin action.

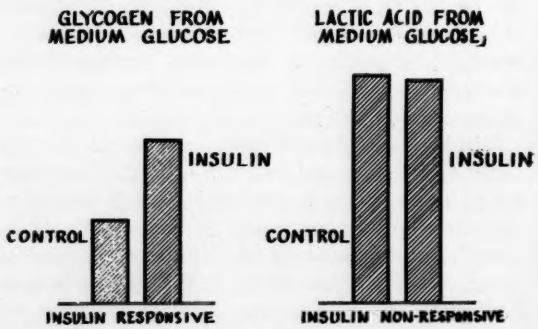

FIG. 6. Two coexisting glycolytic systems in normal rat diaphragms. Data of Shaw and Stadie, 1956.

DEFECTS OF GLUCOSE METABOLISM IN THE DIABETIC LIVER

Before turning to a discussion of the relation of insulin to fat metabolism, I shall present in figure 7 a summary of evidence in the literature indicating that

there is a metabolic block in the early stages of the metabolism of glucose in the diabetic liver.

Much of this evidence has been obtained by the study in vitro of liver slices from diabetic rats or cats using isotopic glucose. In summary, the figure shows that there is a diminished oxidation of glucose by liver, a diminished conversion of glucose to glycogen, a diminished glycogen storage, a depression of the ability of the liver to phosphorylate glucose, a markedly increased new formation of glucose, particularly from unknown precursors presumably protein. It appears clear from the summation of this evidence that a metabolic block in the early stages of the hepatic metabolism of glucose exists in the diabetic. But there is also much experimentation and discussion which centers around the possibility that a second metabolic block exists in the diabetic, affecting adversely the complete oxidation or synthesis of fatty acids. It is possible that part of the impairment of fatty acid synthesis is secondary to impairment of glucose metabolism. But there is evidence which points to a defect in fat synthesis per se. In sum then, we have two distinct areas of metabolic derangement in the diabetic liver, namely, that pertaining to glucose metabolism and that pertaining to fatty acid synthesis. The most striking aspect in these departures from normality in the diabetic liver rests in the fact that no one to my knowledge has ever demonstrated in vitro a reversal toward normal of these defects by the addition of insulin in the equilibrating medium. In the normal liver slice, effects of medium insulin upon fatty acid synthesis from lactate, acetate or pyruvate are easily demonstrable, but here again effects of insulin in vitro upon glucose metabolism have not been demonstrated. This situation is in striking contrast to the case in muscle where, as I shall show later in my discussion of insulin combination, the response to insulin both in diaphragms from the normal or diabetic rats is immediate. This appears to me to be at the base of some fundamental difference in the mechanism of insulin reaction in the two types of tissue. But before discussing this evidence some remarks of a general nature about fatty acid metabolism in the liver would be helpful.

GLUCOSE UPTAKE	DECREASED
CONVERSION TO CO_2	DECREASED
GLYCOGEN FORMATION	MARKEDLY DECREASED
GLUCOSE OUTPUT	MARKEDLY INCREASED
GLUCOSE FROM UNKNOWN SOURCES	MARKEDLY INCREASED

FIG. 7. Departures from normal of the glucose metabolism of liver slices from alloxanized rats. Combined data from the literature.

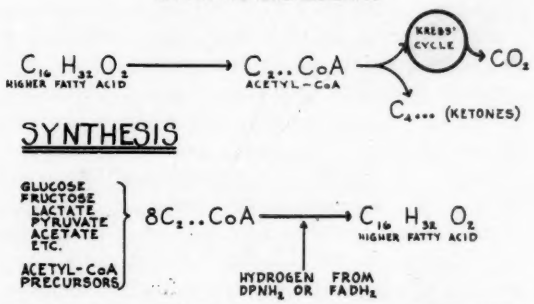

FIG. 8. Metabolic Schema: Fatty acids. Data of Stadie, 1956.

FATTY ACID METABOLISM IN THE DIABETIC LIVER

Our present knowledge of fatty acid synthesis or fatty acid breakdown is presented in a highly schematic way in figure 8.

Higher fatty acids, for example, palmitic acid, a 16-carbon fatty acid, is broken down by successive beta oxidation. This process involves three steps: condensation with coenzyme A, oxidation at the beta carbon, and a splitting off of two carbons to form acetyl-coenzyme A. The acid is now shorter by two carbons. A repetition of this process results in the complete breakdown of the higher fatty acid to acetyl-CoA. In the liver, two fates of the acetyl-CoA are of immediate interest: (1) oxidation through the Krebs' cycle to carbon dioxide, or (2) combination of two acetyl-CoA molecules to form a 4-carbon ketone which is not further metabolized in the liver. The synthesis of higher fatty acids, e.g., palmitic acid, is indicated in the second half of the schema. There are certain precursors of acetyl-CoA. These are glucose, lactate, pyruvate, fructose, or acetate. Acetyl-CoA molecules, by a series of condensations and reductions, are built up step by step into longer and longer chains until the final product, palmitic acid, is synthesized. But it is important to emphasize that the path of synthesis is not entirely the same as the path of oxidation. I shall return to this later.

Lipogenesis in the liver, both in the intact animal and preparations studied in vitro, is depressed in certain nutritional states, e.g., fasting or drastic reduction in carbohydrate intake. In the experimental diabetic animal, lipogenesis is seriously impaired, a phenomenon first demonstrated by the experiments of Stetten and Boxer[11] who studied the incorporation of deuterium into liver and carcass fats.

The impaired lipogenesis observed in the intact dia-

betic animal can be demonstrated with great convenience using liver slices in vitro. I shall review evidence of this type here which yields the conclusion that there is a second block in the diabetic liver leading to defective fat metabolism independent of any defect in glucose metabolism.

For example, in figure 9, I show data of Chaikoff[12] obtained by equilibrating liver slices from diabetic rats in the presence of certain nutrilites. In all cases, the nutrilites were uniformly labeled with isotopic carbon, enabling an identification of the carbon in carbon dioxide or in higher fatty acids. With glucose as the nutrilite, no radioactivity is found in the CO_2, a result fully to be expected and indicating the presence of the first metabolic block at an early stage of glucose metabolism. In addition, there is no fatty acid synthesis from the glucose indicated by the zero in the last column. With fructose as the nutrilite, the production of CO_2 is the same as that observed in the normal rat. Now this means that the formation of acetyl-CoA from fructose is unimpaired in the diabetic. However, there is no synthesis of higher fatty acids from fructose. The same findings are observed with acetate. When isotopic lactate was used, Chaikoff found normal amounts of CO_2 production again indicating a normal production of acetyl-CoA from this nutrilite. But no fatty acid incorporation was observed. Isotopic pyruvate gave essentially the same results. Except in the case of glucose, these data clearly mean that we have all the conditions necessary for fatty acid synthesis, namely, acetyl-CoA formation and a source of hydrogen for purposes of reduction. Nevertheless, higher fatty acids are not synthesized. The conclusion seems inescapable that, independent of glucose metabolism, there is a second block in the diabetic liver impairing the synthesis of fatty acids. From the summation of this evidence, Chaikoff[13] concluded "A second biochemical block must therefore be postulated for the diabetic liver, and the observations with C^{14}-acetate indicate that it lies in the path of conversion of a '2-carbon-like' compound to fatty acids." This metabolic block, so clearly demonstrated in the liver slice of the alloxanized rat, may be eliminated in two ways: (1) by the prior dietary administration of fructose and (2) by the prior administration of insulin. But it is important to note that the results are not the same: Prior fructose feeding restores the ability of the liver slice to synthesize fatty acids from acetate, lactate and pyruvate but does not restore the loss of the ability of the liver slice to oxidize glucose or incorporate it into fatty acid. Insulin treatment, on the other hand, eliminates both metabolic blocks.

At this point, it is necessary to introduce some experimental evidence obtained from studies of the metabolism of slices from the depancreatized cats obtained in our laboratory and in the laboratory of Gurin.[14]

These data are shown in figure 10. In the right hand column are shown data by Stadie, Zapp and Lukens[15] on the ketone formation by cat liver slices. Note that the production of ketone bodies in the depancreatized cat is some six times that observed in the fasting normal cat. On the other hand, the data on the acetate incorporated by the cat liver slice observed by Brady, Lukens and Gurin was essentially zero. This can only lead to one conclusion, namely, that oxidative breakdown of higher fatty acids to acetyl-CoA from which the ketones are formed is unimpaired in the diabetic state; second, that synthesis of fatty acid from acetyl-CoA is impaired. A corollary of these two conclusions is that the two pathways, namely, oxidative breakdown and synthesis of fatty acids, are not the same.

Experiments reported by Shaw from Gurin's laboratory furnish further experimental evidence that there are two pathways of fat metabolism, one of which is impaired in the diabetic. Shaw's[16] critical experiment is shown in figure 11.

He studied fatty acid synthesis by mitochondrial

ISOTOPIC NUTRILITIES	RECOVERED ISOTOPIC CARBON: AS CO_2	AS HIGHER FATTY ACIDS
GLUCOSE	O	O
FRUCTOSE	NORMAL	O
LACTATE	NORMAL	O
PYRUVATE	NORMAL	O
ACETATE	NORMAL	O

FIG. 9. Fatty acid metabolism of slices of liver from diabetic rats. Data of Chaikoff et al., 1951.

	Acetate incorporated by cat liver slices into long-chain fatty acids Brady, Lukens and Gurin (1951) Mg./100 mg. Mean	Ketone formation by cat liver slices Stadie, Zapp and Lukens (1940) Micromoles/kg. cat Mean
Normal cats	2-8	240
Depancreatized cats	0-0.7	1,200
Houssay cats	5	85

FIG. 10. Fatty acid synthesis from acetate and ketone formation by liver slices from normal, depancreatized and Houssay cats. Data of Brady, Lukens and Gurin, 1951; and Stadie, Zapp and Lukens, 1940.

SOURCE OF MITOCHONDRIA	FURTHER ADDITIONS	FATTY ACID SYNTHESIS
NORMAL RAT LIVER	NORMAL LIVER SUPERNATANT	YES
	NONE	NO
	BUTYRYL-CoA	YES
DIABETIC RAT LIVER	NORMAL LIVER SUPERNATANT	YES
	DIABETIC LIVER SUPERNATANT	NO
	BUTYRYL-CoA	YES

FIG. 11. Fatty acid synthesis by hepatic mitochondria from normal or diabetic rats. Data of Shaw and Gurin, 1956. Added cofactors: Mg; citrate; DPN. Precursor of acetyl CoA: Isotopic pyruvate.

preparations made from livers of normal or depancreatized rats. His system consisted of four parts: (1) washed mitochondria either intact or lysed; (2) the supernatant from homogenized liver spun at 100,000 g. to remove all particulate matter; (3) certain cofactors such as Mg., citrate, coenzyme I (viz.: diphosphopyridine nucleotide indicated as DPN) and (4) a precursor of acetyl-CoA, namely, isotopic pyruvate. Figure 11 shows that in the case of mitochondria from normal rat liver, fatty acid synthesis from the isotopic pyruvate occurs when normal liver supernatant is included in the system. But synthetic butyryl-CoA alone gives the same result. Synthesis of higher fatty acids from the pyruvate then occurred at a rate comparable to that observed with normal liver supernatant. With mitochondrial preparations made from diabetic rat liver, the addition of supernatant prepared from the diabetic liver resulted in no fatty acid synthesis from pyruvate. With normal liver supernatant added, fatty acid synthesis did occur. The same, however, was observed with butyryl-CoA alone. In other words, diabetic mitochondria behave like normal mitochondria when butyryl-CoA is present. On the basis of his experiments, Shaw concluded that "butyryl-CoA appears to be able to replace the supernatant fraction of both the normal and diabetic water-soluble systems. It seems reasonable, therefore, to suggest that the diabetic liver is unable to convert pyruvate, acetate or acetyl-CoA to fatty acids, because it cannot convert acetyl-CoA to butyryl-CoA. This involves two oxido-reduction steps which in fatty acid are: (1) the reduction of acetoacetyl-CoA to beta hydroxy butyryl-CoA and (2) the hydrogenation of crotonyl-CoA to butyryl-CoA. The former step requires reduced DPN and the latter, reduced FAD. This failure in the diabetic liver which appears in the supernatant fraction of the liver homogenate may be due to the inability of the soluble enzyme system to supply one or both of these two cofactors." Langdon[17] has recently reported experiments which support the conclusion of Shaw that the pathway of synthesis of fatty acids is different from that of oxidative breakdown. Langdon also localized the divergence of pathways to be between acetyl-CoA and butyryl-CoA.

On the basis of the evidence which I have presented here, it is possible to prepare the schema of fatty acid metabolism shown in figure 12.

I have indicated on the left side of the diagram a fatty acid, palmitic acid, containing 16 carbons. The breakdown or oxidation of the palmitic acid proceeds from left to right by beta oxidation involving condensation with coenzyme-A and successive *b*-oxidations with stepwise formation of acetyl-CoA. In the liver, two fates of acetyl-CoA are of immediate interest: (1) complete oxidation through the Krebs' cycle; or (2) condensation of two molecules of acetyl-CoA to produce the 4-carbon ketone body. As I have shown in the case of the depancreatized cat, ketone formation proceeds at a very rapid rate. Therefore, the enzyme systems and the necessary cofactors of this pathway of fat metabolism are unimpaired by insulin lack. The synthesis of fatty acids, however, from acetyl-CoA derived from precursors such as glucose, lactic acid, acetate, pyruvate, fructose, etc., proceeds by a different pathway. Unlike the pathway of oxidative breakdown, this pathway of fatty acid synthesis is impaired in the diabetic state. The work of Shaw makes it reasonable to assume that the jump from acetyl-CoA to butyryl-CoA is the locus of the

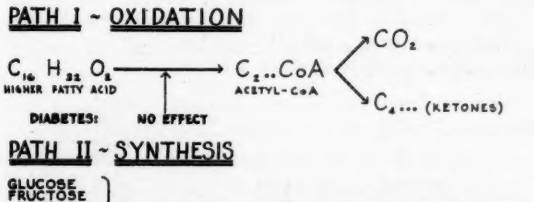

FIG. 12. Schema of fatty acid metabolism in the diabetic animal. Data of Stadie, 1956.

	LEVEL OF PLASMA INSULIN/γ%ml	% RECOVERY OF 100gm U ADDED INSULIN
NORMAL	70-120	100
PANCREATECTOMIZED	0	17
HOUSSAY	0	100
LONG-LUKENS	0	100

FIG. 13. Levels of plasma insulin and insulin inhibitor in normal, diabetic, Houssay, and Long-Lukens cats. Unpublished data: Courtesy of Dr. Vallance-Owen, 1956.

metabolic defect.

The data shown in figure 10 indicate strongly that the system which functions to bridge this gap is impaired in the diabetic state because of the inhibitory action of pituitary factor which becomes manifest owing to lack of insulin. The figure shows data published by Brady, Lukens and Gurin[14] on the incorporation of isotopic acetate by cat liver slices into long chain fatty acids. Note that in the case of the depancreatized cat the incorporation of acetate as a measure of the ability of the liver slice to synthesize fatty acid is essentially zero. On the other hand, ketone formation continues at a rate almost five to six times that observed in the normal cat. In the Houssay cat, however, the removal of the pituitary factor has restored the ability of the diabetic liver slice essentially to its full synthesizing capacity with respect to fatty acids. Note also that ketone formation has fallen to a normal value; in other words, the normal balance of synthesis and oxidation of fatty acids has been restored and homeostasis of fat metabolism in the liver has been reestablished. We conclude from this that the enzyme system bridging the gap from C_2 to C_4 in fatty acid synthesis must be under balanced control of both insulin and pituitary factors.

Supportive evidence for the existence of powerful contra-insulin factor originating in the pituitary is shown by data in figure 13 from Dr. Lukens' laboratory.

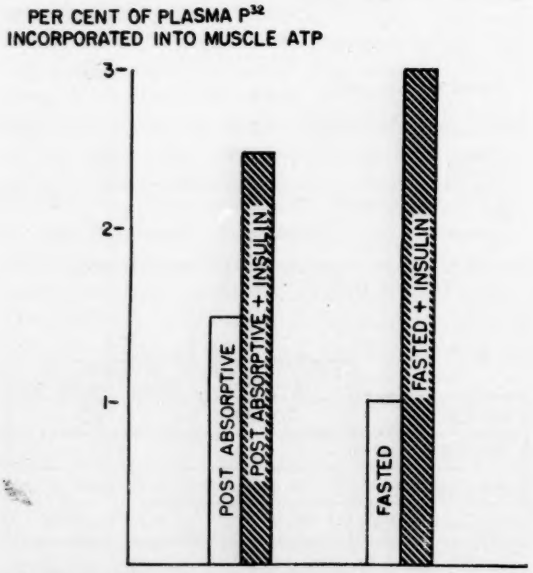

FIG. 14. Effect of insulin upon the incorporation of plasma P^{32} into muscle ATP. Data of Sacks, 1948.

Dr. Vallance-Owen[18] has kindly permitted me to use data of his experiments prior to publication. He has refined the rat diaphragm technic to utilize its characteristic extra glucose uptake in response to insulin as a quantitative method for measuring plasma insulin. His method measures as little as 10 microunits of insulin per ml. of plasma with accuracy. Figure 13 shows in the first column the type of cat preparation used, viz.: normal, depancreatized, Houssay or Long-Lukens. The second column contains the mean value of the plasma-insulin content in microunits per ml. In the normal cat, this ranges from 70-120. In the other three types of preparations, there is no demonstrable insulin. The third column shows the extent to which 1,000 microunits of insulin added to the plasma per ml. can be demonstrated to retain its activity when measured by the diaphragm method. In the case of the normal cat, 100 per cent of the added insulin is demonstrable. In the depancreatized cat, the activity is reduced to approximately 17 per cent. Strikingly, in both the Houssay cat and the Long-Lukens cat, the contra-insulin factor has disappeared from the blood plasma and essentially 100 per cent of the activity of the added insulin may be demonstrated.

In this connection, some data from our laboratory might be cited. Haugaard, Vaughan, and I[19] measured isotopic insulin bound to diaphragms of hypophysectomized rats. We showed that the activity of the bound insulin per microgram in accelerating extra glycogen synthesis was many times greater in the hypophysectomized animal than in the normal. All this evidence indicates that in the plasma, in the liver, and in muscle, insulin and pituitary factors (and presumably adrenal factors also) are in a state of balance which if disturbed by lack of insulin leads to departures from normal types of metabolism characteristic of the diabetic.

PHOSPHATE METABOLISM IN THE DIABETIC ANIMAL

The relation of phosphate metabolism to the diabetic state has long been a matter of interest. Recently, attention has been focused on the phenomenon of oxidative phosphorylation in the diabetic. The oxidation of certain nutrilites through the Krebs' cycle mechanism brings about the incorporation of inorganic phosphate into certain types of organic combinations, for example, adenosinetriphosphate, in such a way that the energy derived from oxidation is incorporated into the phosphate bond. In other words, oxidative phosphorylation results in the formation of compounds containing energy-rich phosphate bonds which are stored in the tissue either as such or as creatine phosphate. These compounds

are sources of energy for a wide variety of activities such as muscular contractions, synthesis of protein or fat, osmotic work, and the like. The possibility that a defect in oxidative phosphorylation decreasing available high energy phosphate might be involved in some of the metabolic defects in the diabetic is a real one and has received considerable attention in the literature. For example, Kaplan and his co-workers[20] studied the incorporation of injected radioactive phosphate into various organic phosphate fractions of the liver and muscle. They found, in general, that insulin brings about an increased turnover rate of isotopic phosphate in these fractions. An example of this type of experiment is shown in figure 14 which is taken from some of the published work of Sacks.[21]

The data show the per cent of plasma P^{32} incorporated into muscle ATP. The two columns on the left indicate the comparison between the rate of incorporation and the post absorptive state without insulin and the hatched column, the post absorptive state with insulin. Similarly, the right hand two columns show analogous data in the fasted preparation. A significant effect of insulin in increasing the turnover rate of P^{32} into muscle adenosinetriphosphate is obvious. Experiments of other types leading to the same conclusion have also been reported in the literature and for illustration I show one.

The data shown in figure 15 are taken from the paper of Charalampous and Hegsted.[22] They studied possible defects of oxidative phosphorylation by determining the rate of acetylation of the foreign amine such as para-aminobenzoic acid in this case. This reaction is known to be dependent upon the availability of ATP. The ordinate shows the per cent of injected para-aminobenzoic acid excreted in the urine in the acetylated form and the abscissa shows the time and days following alloxination. For comparison, the curves obtained in normal rats are also shown, but the lower curves show definitely that as time goes on there is diminished ability of the diabetic rat to acetylate injected para-aminobenzoic acid. From these data, the authors concluded that "it is reasonable to assume that a primary deficiency of ATP formation is the cause of the metabolic defect."

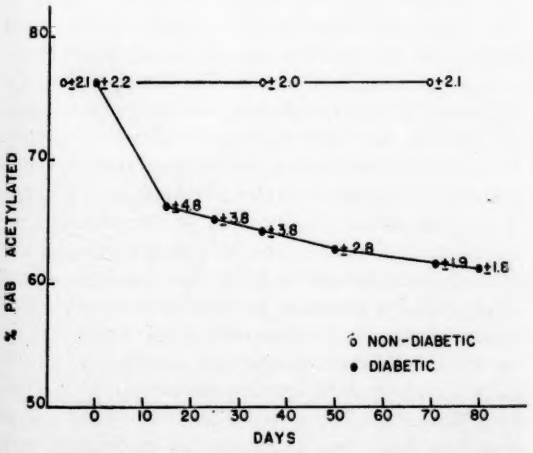

FIG. 15. The acetylation of injected para-aminobenzoic acid into normal and diabetic rats. Data of Charalampous and Hegsted, 1949.

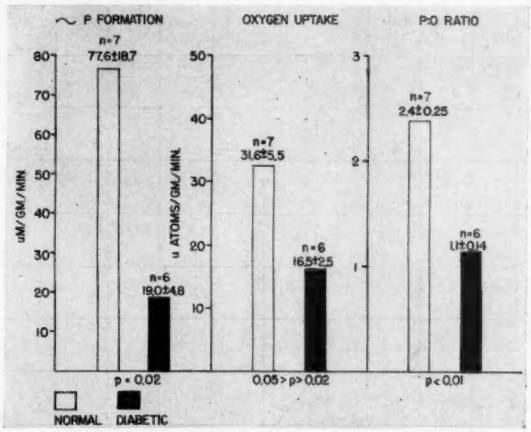

FIG. 16. Oxidative phosphorylation by hepatic mitochondria from normal and diabetic cats. Data of Vester and Stadie, 1956.

This problem in the metabolism of the diabetic animal has long been a subject of interest in our laboratory and recently Vester[23] studied the problem more directly by determining the rate of oxidative phosphorylation by mitochondria prepared from the livers of depancreatized cats.

It is unnecessary to describe the technical details. It suffices to say that the mitochondria were prepared by conventional methods and the assay of their ability to form ATP from inorganic phosphate by the oxidation of pyruvate was done by appropriate methods. The data are expressed in three ways: (1) the left section of the figure shows the rate of formation of ATP per gram of mitochondrial protein per minute in the normal and the diabetic; (2) the middle section shows the oxygen uptake of these respective mitochondrial preparations and (3) the third section on the right shows the ratio between the ATP formed and the oxygen uptake. This so-called P:O ratio measures the efficacy of oxidative phosphorylation by the mitochondria. Figure 16 shows

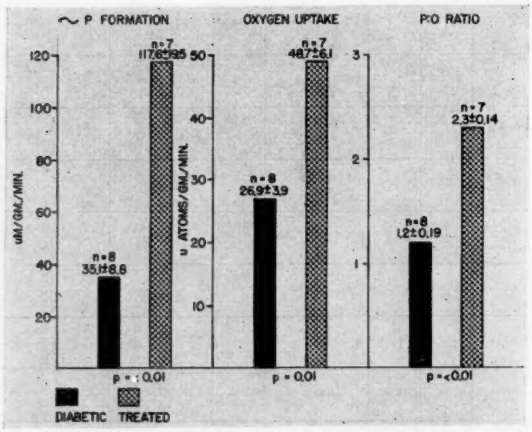

FIG. 17. Restoration to normal of the oxidative phosphorylation by mitochondria prepared from livers of insulin treated depancreatized cats. Data of Vester and Stadie, 1956.

a summary of some of the data. The open columns show the values in the normal mitochondria; the solid columns, the respective values in the diabetic. It is clear that there is a highly significant diminution of oxidative generation of high energy phosphate bonds by mitochondria prepared from diabetic cat livers as compared to those prepared from normal cat livers. These depressions of oxidative phosphorylation were observed in all three types of measurements, namely, total ATP formation, oxygen uptake and P:O ratios.

Vester showed that this defect in oxidative phosphorylation in the diabetic cat was reversed by insulin treatment. His data are shown in figure 17. In these experiments, a biopsy specimen was obtained from the liver when the cat was in a diabetic status, three days post-pancreatectomy. From the biopsy material, mitochondria were prepared and assayed for phosphorylative activity. The cat was then vigorously treated with insulin until essentially restored to normal. The second specimen was taken of the liver and assayed as before. The

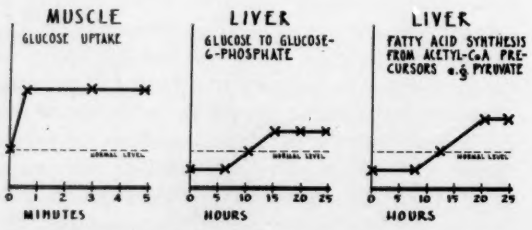

FIG. 18. Sequence of events following injection of insulin into diabetic rats. Data of Renold, Hastings, Nesbett, and Ashmore, 1955.

data obtained are those shown in the previous figure, namely, total formation of ATP, oxygen uptake, and P:O ratios. The solid columns here indicate the diabetic state and the hatched columns, the treated state. It is obvious from the data that insulin has restored essentially to normal the oxidative phosphorylation ability of the hepatic mitochondria of the depancreatized cat. The meaning of these data is not fully manifest and cannot be discussed for lack of time. However, the summation of evidence which I have reviewed, together with that in the literature, indicates that oxidative phosphorylation is impaired in the diabetic status and cannot be ignored as a possible factor for departure of both fat and carbohydrate metabolism from normal.

THE BINDING OF INSULIN[24, 25, 26, 27, 28]

I call your attention briefly to a phenomenon which I believe will eventually be the axis about which a complete theory of the action of insulin will revolve. I refer to the phenomenon known as the binding of insulin on tissues. A few remarks will indicate why theory predicts this phenomenon and experiment demonstrates it. Chemical reactions do not occur between molecules which are separated by distances greater than molecular dimensions. Since I think it is obvious that insulin influences metabolism through effects on enzyme systems, it can hardly do so without becoming chemically bound to the enzyme system. Otherwise, we would have to imagine chemical action at a distance and this is inadmissible. This means that chemical combination of insulin with tissues is a prerequisite to insulin action. The demonstration of insulin binding is simple and the rat diaphragm serves admirably since it is known to react quite constantly to the presence of insulin. A normal rat diaphragm is dipped momentarily into a solution of radioactive insulin. The binding of insulin by tissue is a very rapid process. As little as ten seconds' exposure of the diaphragm to a solution of insulin suffices. Subsequent prolonged washing does not eliminate the radio-isotopic insulin and when the diaphragm is equilibrated in glucose there is always found the customary significant increase in glycogen synthesis and glucose uptake brought about by the minute amounts of isotopic insulin which can be demonstrated to be bound to the diaphragm. This phenomenon of insulin binding by tissue has been demonstrated also in the case of adipose tissue and the lactating mammary gland of the rat. Many experiments which need not be reviewed here have been done to demonstrate the characteristics of bound insulin. It suffices to say that bound insulin possesses the properties customarily assigned to insulin,

namely, decrease of activity in the diabetic animal, marked increase of the activity in tissues of the hypophysectomized animal, depression of its activity by prior injection of growth hormone plus cortisone, etc. Recently, Stetten[29] has treated the phenomenon from the mathematical point of view in an endeavor to apply the mass action concept. I mention this topic for the purpose subsequently to refer to it in integrating the known actions of insulin in different types of tissue.

METABOLIC ADAPTATION TO INSULIN

The rapidity with which bound insulin achieves its metabolic effects is in contrast to another aspect of insulin action which may be loosely defined as metabolic adaptation. By adaptation, I mean that a change in the function of enzymatic systems of tissues occurs which requires considerable time for full development. Let me illustrate by data taken from experiments with liver slices and the intact animal. Zapp, Lukens, and I[14] showed, some years ago, that the marked ketone formation shown by depancreatized cat liver slices in vitro was uninfluenced by the mere addition of insulin to the medium. However, the preadministration of insulin to the cat for a period of time of at least six to twenty-four hours and in sufficient doses to give a substantial diminution of the hyperglycemia resulted in a sharp diminution of ketone formation in vitro by liver slices prepared at the end of the treatment period. Chaikoff,[30] using alloxanized rats, showed that the restoration of the ability of the liver slice to incorporate acetate into higher fatty acids required prolonged treatment up to at least six to twenty-four hours. Hastings[31] with his co-workers has studied this phenomenon at considerable length. Their results, in the case of the diabetic rat, are shown in figure 18. Note that in the case of muscle, represented by the diaphragm, the response of injected insulin was immediate (a minute or less), manifested by an increased uptake of glucose from the medium and an increased glycogen synthesis. Liver slices from the same rat, however, responded to the injected insulin very slowly so that periods of time, minimally six hours and often up to twenty-four hours for full effect, were required to show restoration of the functions enumerated in the figure, namely, total phosphorylation of glucose, net glycogen formation from glucose, fructose, pyruvate, and acetate, oxidation of these same metabolites or the incorporation of the carbon from these substances into the higher fatty acids.

These relations are so strikingly different from those observed in the case of the muscle that it is not unreasonable to conclude that different mechanisms are operative. In the case of the diaphragm, the insulin action is essentially instantaneous and appears to be concerned with transport of glucose. In the liver, insulin action is slow. By some mechanism which still remains to be clarified, insulin permits the liver slowly to complete an enzyme system which, in the absence of the insulin, has lost its function in whole or in part. This completion or adaptation is one which may require synthesis, perhaps of new proteins as enzymes, introduction of formation of new cofactors such as triphosphopyridinenucleotide, or possibly by some interaction with opposing hormones such as the pituitary or the adrenals. These reactions take time and furthermore suggest the possibility of diverse types of insulin action in the liver, respectively glucose metabolism or fatty acid synthesis.

UNIFIED CONCEPT OF INSULIN ACTION

On the basis of the evidence which I have reviewed this morning, I have formulated what I call a unified concept of insulin action which is shown in figure 19. The figure shows four columns: tissue, mechanism of action, site of action, and chief metabolic effects. The tissues considered are muscle, liver, adipose tissue, brain and other. In muscle, the mechanism of action may be considered to involve chemical combination and the site of action is presumably upon cell surfaces. The effect is immediate and the chief metabolic action is to accelerate glucose transport. Entrance of glucose into the cell initiates further enzymatic action. In the liver, the mechanism of action is that of adaptation and the site of action is presumably on enzyme systems within the interior of the cell. The site of action may be multiple and may involve neutralization of contra-insulin pituitary or adrenal factors. The time required for complete restoration to the normal state is long, varying from six to twenty-four hours. Again the chief metabolic

TISSUE	MECHANISM OF ACTION	SITE OF ACTION	CHIEF METABOLIC EFFECTS
MUSCLE	COMBINATION	CELL SURFACES	GLUCOSE TRANSPORT *et seq.*
LIVER	ADAPTATION	ENZYME SYSTEMS: CONTRA PITUITARY	GLUCOSE OXIDATION, etc; FATTY ACID SYNTHESIS; OXIDATIVE PHOSPHORYLATION (?)
ADIPOSE	ADAPTATION	ENZYME SYSTEMS	GLUCOSE OXIDATION, etc; FATTY ACID SYNTHESIS
BRAIN	NO DEMONSTRATABLE ACTION		
OTHER	INSUFFICIENT DATA		

FIG. 19. Unified concept of insulin action. Data of Stadie, 1956.

effect may be multiple, involving (1) glucose oxidation, glucose uptake and other glucose metabolic actions and (2) re-establishment of fatty acid synthesis from two carbon fragments derived either from carbohydrate or other sources. The locus of action here presumably is between a C_2 and a C_4 carbon complex. Oxidative phosphorylation is restored to normal but whether this defect is part of the diabetic picture cannot be said with assurance now. In adipose tissue the effects are somewhat similar to those observed in the liver, namely, a mechanism of action involving adaptation upon enzyme systems within the cell proper. Restoration is slow and the effects are again those of restoring glucose metabolism and fatty acid synthesis to normal. In the case of the brain, there has been no demonstrable effect either of the diabetic state or of injected insulin. In other types of tissues, the data are insufficient to draw conclusions.

I have no illusion that this concept is complete or final or even free of error, but to me it is meaningful and provocative. The validity of an hypothesis is of little significance. The questions which it prompts and the experiments which it helps to project are what count. If the concept accomplishes a little in this direction, it will have served its purpose.

SUMMARY

Current views on the metabolic defects in the diabetic animal and the mechanism of the action of insulin are discussed.

Transport of glucose and other sugars across cell membranes of muscle and adipose tissue to sites of enzyme action is dependent upon insulin and hence is slow in the diabetic. Further metabolism (e.g., oxidation) therefore is markedly impaired. Insulin accelerates transport of sugars with the characteristic structure of glucose in carbons 1, 2 and 3. Insulin responsiveness is shown by: (1) increase of volume of distribution of injected sugar by simultaneous injection of insulin in eviscerate dogs; (2) increased rate of penetration of glucose into aqueous humour across ciliary body of the eye; (3) increase by insulin of intracellular free glucose of muscle both in vivo and in vitro. In sum: transport (a reaction antecedent to phosphorylation) is accelerated by insulin rather than the hexokinase reaction.

Defects of hepatic glucose metabolism occur in the diabetic animal, viz.: diminished oxidation, decreased phosphorylation, decreased glycogen synthesis, increased phosphatase action, increased gluconeogenesis from protein.

Synthesis by liver of higher fatty acids from acetyl-CoA precursors, e.g., glucose, fructose, lactate, pyruvate, acetate, etc., is seriously impaired in the diabetic. Fatty acid breakdown by oxidation to ketone acids is markedly increased. These two defects of fatty acid metabolism are not present in the Houssay animal. Together with other evidence this indicates that synthesis follows a different pathway from oxidative breakdown. Only the first pathway is impaired in the diabetic and the defect involves the step between acetyl-CoA and butyryl-CoA.

Insulin in the diabetic rapidly restores muscle metabolism to normal both in vivo and in vitro. But restoration in the liver (by adaptation of enzyme systems) requires longer periods (six to twenty-four hours) of intensive treatment in the intact animal. The role of insulin binding by tissues in this differentiation of response to insulin is discussed.

The formation of high energy phosphate bonds by mitochondria from diabetic cat livers is impaired. This diminished formation of stored chemical energy in the form of adenosinetriphosphate may be an important factor in the diabetic state.

The evidence discussed is integrated into a unified concept of the action of insulin on mammalian metabolism.

SUMMARIO IN INTERLINGUA

Recente Progressos in le Recerca de Insulina: Conferentia Commemorative Banting

Es discutite le currente ideas super le defectos metabolic in le animal diabetic e le mechanismo del action de insulina.

Le transporto de glucosa e de altere sucros trans le membranas cellular de texitos muscular e adipose al sitos de action enzymic depende de insulina e per consequente es tarde in le diabetico. Consequentemente le metabolismo ulterior (e.g., oxydation) es marcatemente deteriorate. Insulina accelera le transporto de sucros que ha le structura characteristic de glucosa in le carbones 1, 2 e 3. Reactivitate a insulina se monstra per: (1) augmentate volumine de distribution de injicite sucro, obtenite in canes eviscerate per le simultanee injection de insulina; (2) accelerate penetration de glucosa a in le humor aquee trans le corpore ciliari del oculo; (3) augmento per medio de insulina del libere glucosa intracellular de musculo e in vivo e in vitro. In summa: transporto (un reaction antecedente a phosphorylation) es accelerate per insulina plus tosto que per le reaction a hexokinase.

Defectos del metabolismo de glucosa hepatic occurre in le animal diabetic, a saper: oxydation diminuite, phosphorylation diminuite, diminuite synthese de glycogeno, augmentate action de phosphatase, augmentate gluconeogenese ab proteina.

In le diabetico es gravemente deteriorate le synthese hepatic del acidos grasse superior ab le precursores de acetyl-CoA, e.g., glucosa, fructosa, lactato, pyrovato, acetato, etc. Le conversion per oxydation de acidos grasse a acidos cetonic es marcatemente augmentate. Iste duo defectos del metabolismo de acidos grasse non es presente in le animal de Houssay. Insimul con altere datos isto indica que le synthese seque un altere via que le lyse oxydative. Solmente le prime de iste vias es deteriorate in le diabetico, e le defecto concerne le passo inter acetyl-CoA e butyryl-CoA.

In le diabetico insulina rapidemente restaura al nivello normal le metabolismo de musculo e in vivo e in vitro. Sed in le hepate le restauration (per medio de adaptation del systemas enzymic) require periodos plus extendite (de sex a vinti-quatro horas) de tractamento intense in le animal intacte. Es discutite le rolo del fixation de insulina per le texitos que es exhibite in iste differentiate responsa a insulina.

In mitochondrios ab le hepate de cattos diabetic es deteriorate le formation de ligamines phosphatic a alte energia. Iste diminuite formation de immagazinate energia chimic in le forma de adenosino-triphosphato pote esser un factor importante in le stato diabetic.

Le datos discutite es integrate in un concepto unificate del action de insulina in le metabolismo mammalian.

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A Newer Pathway of Carbohydrate Metabolism; The Pentose Phosphate Pathway

Paul A. Marks, M.D., New York*

In the past thirty years a vast body of information has been compiled relating to carbohydrate metabolism. Nevertheless, it is becoming increasingly evident that the elucidation of the metabolic disturbance in diabetes mellitus requires an even more complete knowledge than is presently available of the complex chemical routes followed by glucose in its conversions and interactions with other cell components. In this area of carbohydrate metabolism most gratifying progress has been made with the demonstration of previously unsuspected pathways of glucose utilization. Until rather recently, it was generally believed that the primary, if not the sole, route of glucose breakdown by mammalian tissue was via the Embden-Meyerhof or anaerobic-glycolytic pathway involving the conversion of glucose to pyruvate and lactate and its subsequent oxidation to CO_2 by the citric acid cycle. Evidence has now accumulated to indicate the existence of at least one new pathway of glucose metabolism, referred to as the pentose phosphate pathway, or the hexose monophosphate oxidative shunt, which may often supplement significantly the anaerobic-glycolytic scheme. Before turning to some of the details and possible significance of this alternate pathway, a brief review of the reactions of glycolysis and the citric acid cycle is desirable.

ANAEROBIC GLYCOLYSIS AND THE CITRIC ACID CYCLE

The exact mechanism of glucose transport across the cell membrane is not well understood.[1] Certain of the reactions of intracellular glycolysis, however, are well established and are summarized in figure 1.[2] The first step in the metabolism of glucose is its conversion to the phosphorylated form, glucose-6-phosphate. This reaction is catalyzed by the enzyme hexokinase and requires as a source of energy and phosphate, adenosine triphosphate (ATP). It is essentially an irreversible reaction.

Presented at the meeting of the Clinical Society of the New York Diabetes Association on Feb. 23, 1956.

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Glucose-6-phosphate has a key position in glycolysis and may have one of several fates.[3] Normally, a small percentage of the glucose-6-phosphate in liver and muscle is converted to glycogen. Liver possesses the enzyme, a phosphatase, necessary for the conversion of glucose-6-phosphate to free glucose. As a result of the presence of this enzyme in liver, this organ is the only major endogenous source of free glucose.

The greatest portion of glucose-6-phosphate, under normal circumstances, is broken down via several intermediates, including fructose-6-phosphate and triose phosphate, to pyruvate and lactate. This is the series of reactions involved in anaerobic glycolysis.

The subsequent metabolism of pyruvate is summarized in figure 1.[4] Pyruvate may be oxidatively decarboxylated to form acetyl coenzyme A which, in turn, condenses with oxalacetate to form citric acid in the tricarboxylic acid cycle. In addition, pyruvate may enter the citric acid cycle directly by a carboxylation reaction to form a dicarboxylic acid precursor of oxalacetate. The major portion of glucose metabolized to pyruvate is converted by means of the reactions of the citric acid cycle to either CO_2 and H_2O or is made available by this cycle for amino acid and ultimately protein synthesis. Acetyl coenzyme A, the so-called activated two-carbon fragment, plays a key role in the crossroads of sugar and fat metabolism. Acetyl coenzyme A is the building block in fatty acid synthesis.[5] The synthesis of fatty acids is a reductive synthesis requiring hydrogen in the form of reduced diphosphopyridine nucleotide (DPNH), which is generated in glucose breakdown by anaerobic glycolysis and the citric acid cycle. Perhaps hydrogen in the form of reduced triphosphopyridine nucleotide (TPNH) may also play a role in fatty acid synthesis. As we shall presently discuss in some detail, TPNH is generated by glucose oxidation via the pentose phosphate pathway.

In experimental diabetes mellitus it has been demonstrated that in addition to the block in glucose utilization at the level of glucose conversion to glucose-6-phosphate, there is a decrease in the synthesis of fatty acids from acetate.[6] The relationship between these two

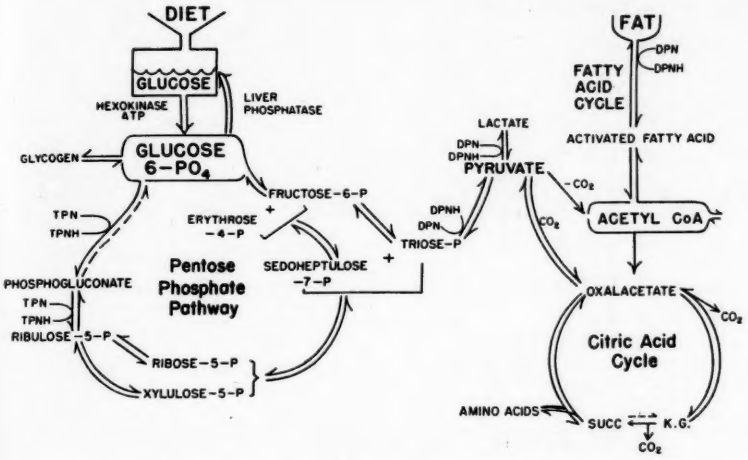


FIGURE 1

metabolic defects is not clear. It may be that in diabetes the block to glycolysis results in an inadequate supply of the hydrogen in the form of DPNH or TPNH necessary to fatty acid synthesis.

PENTOSE PHOSPHATE PATHWAY

Let us now turn our attention to the reactions involved in the alternate pathway of glucose metabolism. The recognition of this newer pathway of glucose utilization, perhaps one of the most exciting of the recent developments in carbohydrate metabolism, is the result of work by many investigators, dating from the studies in the thirties by Warburg,[7] Lipmann,[8] Dickens,[9] and Dische[10] and, more recently, by Horecker,[11] Racker[12] and others. This pathway is referred to as the hexose monophosphate oxidative shunt, because the initial steps involve the direct oxidation of glucose-6-phosphate, or the pentose phosphate pathway, since 5-carbon sugars, i.e., pentoses, are intermediates in this pathway. The individual reactions involved in this cycle are summarized in figures 2-7. They will be discussed briefly, for the details of the reactions are not important to the present purpose. This discussion will primarily indicate certain of the distinctive aspects of this cycle, as well as its possible relationship to the over-all picture of carbohydrate metabolism.

The first step in glucose metabolism by the alternate cycle is identical with that of anaerobic glycolysis, namely, its phosphorylation to glucose-6-phosphate. The oxidation of glucose-6-phosphate results in its conversion to 6-phosphogluconolactone, the ring form of 6-phosphogluconate.[13] 6-phosphogluconate has a carboxy instead of an aldehyde group in position one. This oxidation requires triphosphopyridine nucleotide (TPN) and generates the reduced form of this cofactor, TPNH (figure 2). 6-phosphogluconate is in turn oxidized to the 5-carbon keto sugar, ribulose-5-phosphate.[14] In this oxidative step, CO_2 is formed and, again, TPN is required and TPNH generated (figure 3).

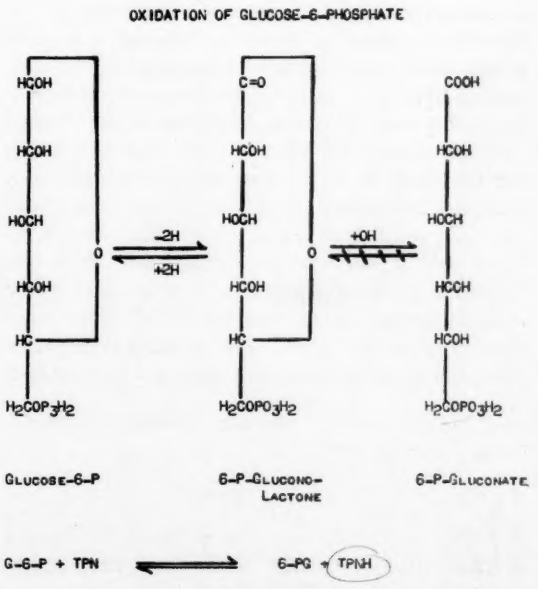
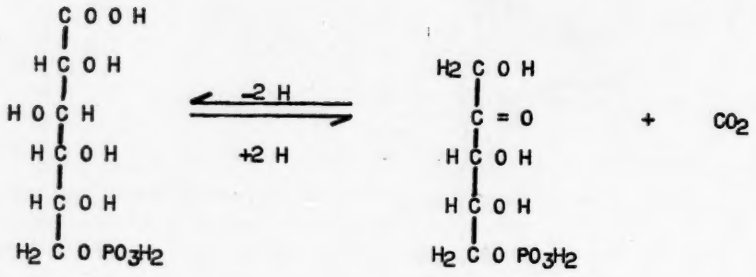


FIGURE 2

OXIDATION OF 6-PHOSPHOGLUCONATE



6-P-GLUCONATE RIBULOSE-5-P

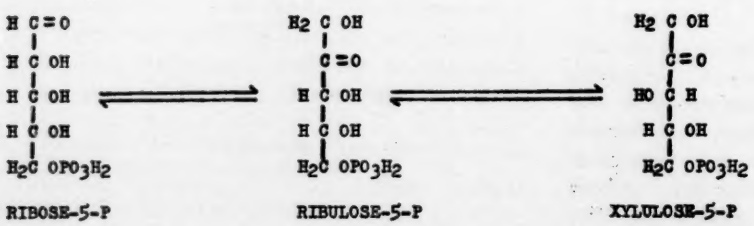
FIGURE 3

$$6\text{-PG} + \text{TPN} \rightleftharpoons \text{Ru-5-P} + \text{TPNH} + CO_2$$

The two steps that have been discussed are oxidative reactions. The subsequent reactions of this pentose phosphate pathway are anaerobic reactions. Recent evidence indicates that the pentoses involved in the next reaction are ribose-5-phosphate and xylulose-5-phosphate.[15, 16] As indicated in figure 4, these 5-carbon sugars are conversion products of ribulose-5-phosphate. In the next reaction (figure 5), catalyzed by the enzyme transketolase,[17, 18] the two top carbons of the keto sugar, xylulose-5-phosphate, are transferred to ribose-5-phosphate with the formation of a 7-carbon sugar, sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate. Until several years ago, sedoheptulose was a rare laboratory curiosity found only in plants of the sedum family. It is now recognized to be widespread in its occurrence, and of great importance in the metabolism of almost every form of plant and animal life. Sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate can be converted, in a reaction catalyzed by the enzyme transaldolase, to the 6-carbon sugar, fructose-6-phosphate and a newly recognized 4-carbon sugar, erythrose-4-phosphate,[19] (figure 6). Fructose-6-phosphate, by reactions identical to those of anaerobic glycolysis, may be converted to fructose-diphosphate and then to two 3-carbon moieties, or converted back to glucose-6-phosphate. The 4-carbon sugar appears to be a highly reactive compound. One reaction which it can undergo is catalyzed by transketolase and involves another molecule of the 5-carbon keto sugar, xylulose-5-phosphate,[15] (figure 7). The products of this reaction are fructose-6-phosphate and glyceraldehyde-3-phosphate, whose possible subsequent fates have been indicated.

The sum of all these reactions is schematically represented in figure 8. For each turn of this complete series of reactions, three glucose molecules are phosphorylated by ATP and there result three molecules of carbon

PENTOSE INTERCONVERSIONS



RIBOSE-5-P RIBULOSE-5-P XYLULOSE-5-P

FIGURE 4

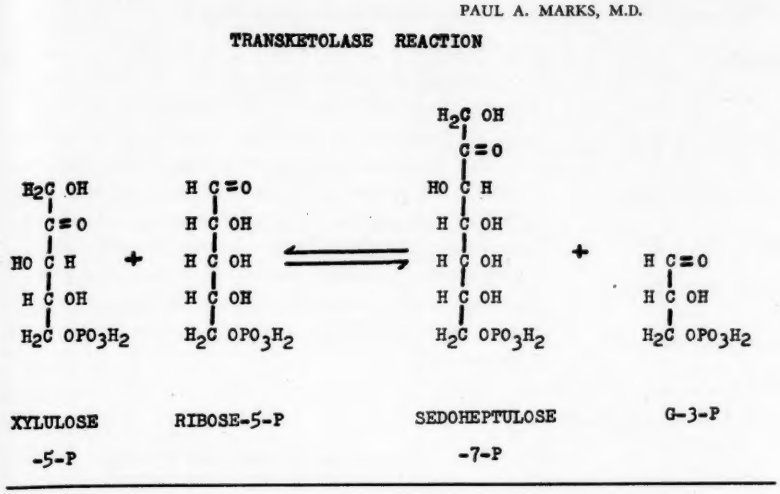


FIGURE 5

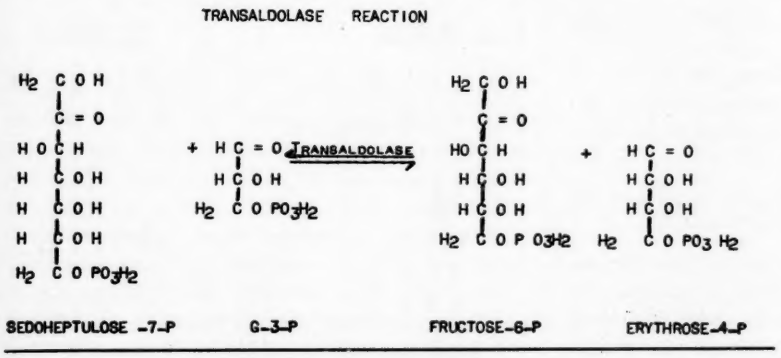


FIGURE 6

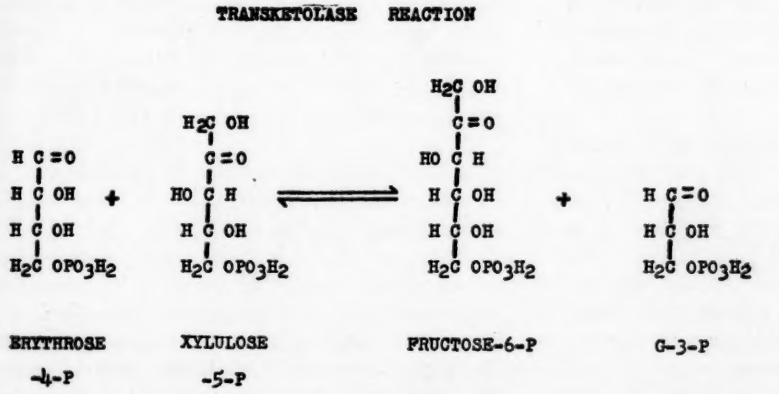


FIGURE 7

dioxide representing the oxidation of half a molecule of glucose. The other half appears as triose phosphate which may either be oxidized to CO_2 via the citric acid cycle or be reconverted to glucose-6-phosphate. In addition, two molecules of a 6-carbon sugar are regenerated. Thus, repeated cycling of this series of reactions, in which several new intermediates participate, can result in the complete oxidation of glucose to CO_2 and H_2O.

The relationship between the reactions of the pentose

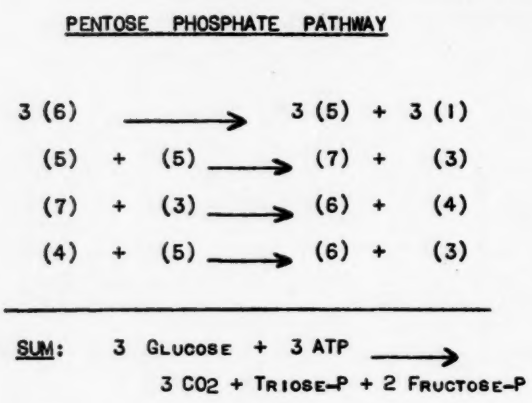


FIGURE 8

phosphate pathway and anaerobic glycolysis can be seen in figure 1. Both pathways share certain intermediates, namely, glucose-6-phosphate, fructose-6-phosphate and triose phosphate. Both schemes, however, represent distinct sets of reactions catalyzed by a separate series of enzymes.

THE ROLE OF PENTOSE PHOSPHATE PATHWAY IN CARBOHYDRATE METABOLISM

Evidence has accumulated to indicate that the enzymes of the alternate cycle, as those of anaerobic glycolysis, are present in most animal tissues.[20] Skeletal muscle alone, of the many normal tissues examined to date, appears to possess pentose pathway enzymes in low concentration. In alloxan diabetic rats, it is reported that the enzymes which catalyze the oxidation of glucose-6-phosphate and 6-phosphogluconate are markedly reduced.[21]

The elucidation of these alternate pathways of glucose metabolism has primarily resulted from work with cell-free systems and frequently isolated enzymes. The investigator is now faced with the task of attempting to assess the relative importance of these various routes of glucose utilization in the intact cell and the total organism. This is an even more difficult, albeit fundamental, problem and one for which there are only the most fragmentary answers at this time.

The availability of isotopic tracer procedures using C^{14}-labeled compounds, has made an approach to this problem possible. In this approach, one may take advantage of the fact that carbon atoms of glucose will have different fates in the two pathways. In the Embden-Meyerhof scheme, glucose-6-phosphate is converted to two molecules of pyruvate in such a fashion that position 1 and 6, 2 and 5, and 3 and 4 give rise to the same carbon atoms of pyruvate (figure 9). Thus, in the subsequent oxidation of pyruvate to CO_2, radioactivity originally in positions 1 and 6 of glucose is assumed to appear in CO_2 at an equal rate. On the other hand, in the pentose phosphate pathway, CO_2 arises from position 1 of glucose, while carbon atoms 2-6 give rise to pentose phosphate. Thus, via the alternate pathway, radioactivity originally present in carbon atom 1 of glucose would presumably appear in CO_2 at a more rapid rate than radioactivity in carbon atom 6 of glucose.

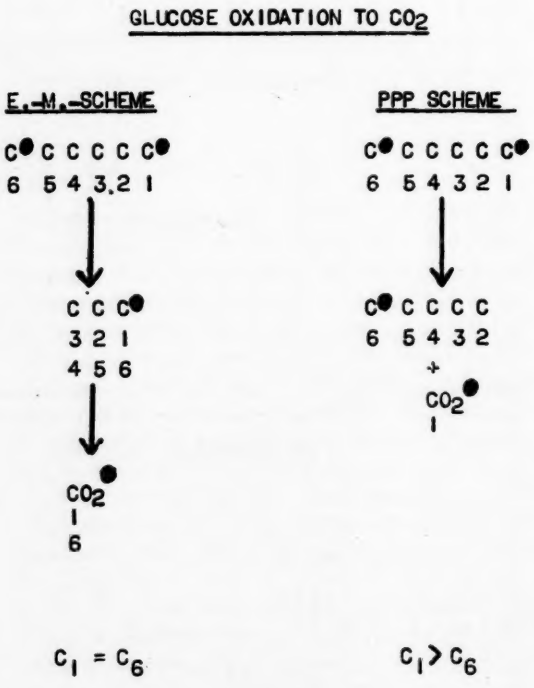


FIGURE 9

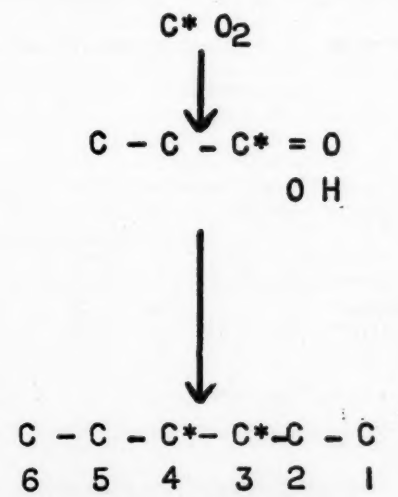
With these theoretical considerations, and a variety of complex mathematical formulations, several investigators using C^{14}-labeled glucose and other specifically labeled intermediates, have attempted to estimate the relative significance of the Embden-Meyerhof and alternate pathways in the oxidation of glucose.[22-28] The results of some of these studies are summarized in table 1. These studies were carried out in vitro with tissue slices from rats or mice. The difficulties encountered

TABLE 1
Pathways of glucose oxidation

Tissue	Embden-Meyerhof Per cent	Pentose phosphate per cent	Reference
Normal			
Liver, rat and mouse	20-98	2-80	22, 23, 24
Kidney, rat	72-100	0-28	22, 23
Heart, rat	100	0	25
Brain, rat	100	0	25
Skeletal muscle, rat	100	0	22, 23
Spleen, mouse	63	37	27
Diabetic			
Liver, rat	51-73	27-49	26
Tumors			
Mammary carcinoma, mouse	82	18	25
Ascites TA_3 carcinoma, mouse	32-77	68	25
Hepatoma 98/15, mouse	100	0	25
Sarcoma 37, mouse	57	43	25
Gardner lymphosarcoma	68	32	27
Ehrlich ascites tumor	77	23	27

in the measurements designed to assess the alternate pathways are complex and it appears that these results must be interpreted with caution.[29] They do give some index of the relative order of magnitude of the two pathways. In normal rat liver, it has been reported that as much as 80 per cent of the glucose oxidized to CO_2 can be metabolized via the pentose phosphate pathway. This figure has been found to vary between 2 and 80 per cent depending somewhat on the method employed in its estimation.[22, 24] On the other hand, brain, heart and skeletal muscle appear to utilize only the Embden-Meyerhof scheme. Diabetic rat liver oxidized glucose to CO_2 via the pentose phosphate pathway to approximately the same extent as normal rat liver.[26] In the several tumor tissues studied, as is indicated in table 1, a rather wide range of patterns has been observed.

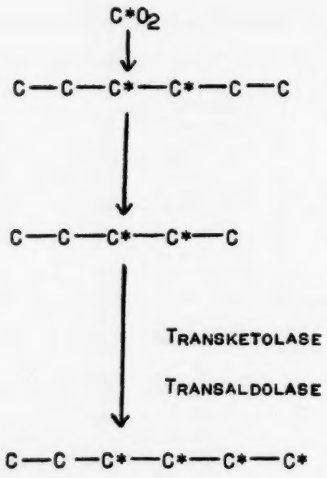
In addition to this effort at evaluation of the relative significance of these pathways in glucose oxidation to CO_2, their role in glycogen synthesis has been investigated. These studies are based upon the predictable differences in the pattern of incorporation of C^{14} into the carbon chain of glucose.[30] Thus, if the Embden-Meyerhof scheme accounts for glycogen synthesis, incubation of liver slices in the presence of $C^{14}O_2$ would be expected to result in incorporation of radioactivity predominantly into carbon atoms 3 and 4 of glucose (figure 10). On the other hand, if the pentose phosphate pathway contributed to glycogen synthesis, C^{14} of CO_2 would be expected to be incorporated into positions 1-4 of glucose (figure 11). In studies with liver slices from both normal and fasted rats, it was found



PREDICTED PATTERN OF $C^{14}O_2$ INCORPORATION IN GLUCOSE VIA EMBDEN-MEYERHOF PATHWAY

FIGURE 10

that radioactivity was incorporated mainly into positions 3 and 4. Less than 5 per cent of the total radioactivity incorporated into glycogen was found in carbon atoms 1 and 2 (table 2).[31] These findings are in agreement with those of Bernstein et al.,[32] who reported that the administration of $C^{14}O_2$ to intact rats yielded glycogen labeled predominantly in positions 3 and 4. It would seem, therefore, that under these conditions glycogen syn-



PREDICTED PATTERN OF $C^{14}O_2$ INCORPORATION IN GLUCOSE VIA PENTOSE PHOSPHATE PATHWAY

FIGURE 11

TABLE 2
Pattern of $C^{14}O_2$ incorporated into rat liver glycogen

	Per cent of total radioactivity					
Carbon atom	1	2	3	4	5	6
Normal rat	2	2	41	52	2	1
Fasted rat	2	1	47	48	1	1

thesis proceeds predominantly via the Embden-Meyerhof scheme.

It is obviously premature to attempt to evaluate the significance of the pentose phosphate pathway in mammalian metabolism. Nevertheless, there are several possible roles of this pathway which may be indicated. It has been demonstrated that the pentose phosphate pathway provides a cycle for glucose oxidation which may operate in certain tissues as a supplement to anaerobic glycolysis and the citric acid cycle. However, the available evidence indicates that this alternate pathway plays a small role, if any, in hepatic glycogen synthesis. The reactions of the pentose phosphate pathway provide a mechanism for the biosynthesis of ribose phosphate.[1] This may prove to be one of its most significant features, since ribose phosphate is a constituent of several cell components, including nucleic acids and various coenzymes. The oxidative steps of this cycle generate hydrogen in the form of TPNH which may play an important role in certain reductive reactions of the body. In addition, recent evidence indicates that the 7-carbon sugar, sedoheptulose, is a carbon source of aromatic amino acids.[33] Perhaps the most well established role of this pathway, and clearly an exceedingly important one, is in the process of photosynthesis. Certain reactions of this alternate cycle provide the mechanism for the generation of the substrate, ribulose-diphosphate, for CO_2 fixation in the synthesis of carbohydrates by green plants.[34]

The discovery of this new pathway of carbohydrate metabolism has perhaps complicated rather than simplified the present efforts at an understanding of the metabolic defect in diabetes. The view of glucose metabolism which recognized a few hexoses and trioses, is now broadened to include 4, 5 and 7-carbon sugars. In addition, it is probable that several pathways differing from the Embden-Meyerhof and citric acid cycle may play a role in mammalian glucose metabolism. Certainly with the discovery of each new pathway, the assessment of the relative significance of these many reactions in the total metabolism of the organism becomes a most difficult task. It is none the less a challenging and fundamental problem which may be solved by newer technics and knowledge.

SUMMARIO IN INTERLINGUA

Un Nove Via del Metabolismo de Hydratos de Carbon; Le Via de Pentosa-Phosphato

Al tempore presente il es un facto ben establite que le metabolismo de glucosa in histos mammalian pote progreder per vias altere que le via del glycolyse anaerobe e del cyclo de acido citric. Recente observationes indica que le reactiones de un tal via alternative—le via de pentosa-phosphato o le derivation oxydative a hexosa-monophosphato—include sucros a quatro, cinque, e septe carbones in ultra del triosas e hexosas. Iste via alternative es catalysate per un serie de enzymas que es distincte ab le enzymas del glycolyse anaerobe o del cyclo de acido citric.

Il es non ancora possibile evalutar le signification del via de pentosa-phosphato in le metabolismo mammalian. Tamen, il existe certe constatationes que indica que sub certe conditiones illo ha un rolo importante in le oxydation de glucosa sed non in le synthese hepatic de glycogeno. In plus, il es possibile que le reactiones del via de pentosa-phosphato provide un mechanismo pro le synthese de ribosa e pro le generation de reducite nucleotidos triphosphopyridinic.

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Massive Insulin Hypoglycemia and Capillary Vascular Physiology in Man

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The vascular responses attending major insulin hypoglycemic reactions in man have been reviewed by Kalinowsky and Hoch,[1] Bellak,[2] and others, but the special role of the capillary and other small vessels has received little attention. The importance of this role is implied in the investigations made on the influence of insulin in coma-provoking doses in regard to brain metabolism, the literature on which has been reviewed by Himwich,[3] and since the capillary system is the final common path by which energy is transferred between blood elements and tissue cells.[4, 5]

This paper is concerned with the acute responses of the minute vasculature of two nondiabetic human subjects receiving massive doses of insulin five times weekly, over a three-month period. The more chronic vascular effects of this sequential experience of hypoglycemia are reported elsewhere.[6]

PROCEDURE

Clinical Material. The subjects were two white male schizophrenics. Patient A was aged 21 years and diagnosed as a catatonic; Patient B was 23 years old and diagnosed as a paranoid schizophrenic. Each was investigated for three months prior to the administration of insulin in order to determine his baseline status. The two patients were then followed through a course of hypoglycemic episodes, brought about by injections of up to 600 units of regular insulin, resulting in sixty sopor reaction states and forty-six coma states in Patient A, and fifty-seven sopors and thirty comas in Patient B. Duration of coma was five minutes per treatment initially, but was allowed progressively to endure up to thirty minutes on any one occasion in each patient. Interruption of the hypoglycemia was accomplished routinely by the oral route in the early sopor stages, by gastric tube in the later sopor and light coma stages, and intravenously in the later deep coma episodes.

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METHODS

Acral blood flow in the arterioles was estimated indirectly by skin temperature measurements taken from the dorsum of the fingers near the nail fold. A Baird-Hardy dermal radiometer was used. Capillary blood flow was measured directly as the rate per second of corpuscular streaming in the nailfold skin capillary loops under microscopic observation, timing being achieved by stroboscopic control in accordance with a method recently introduced.[7] Capillary blood pressure was estimated as the skin-color-disappearance-pressure by means of a glass Hooker capsule affixed to the dorsum of the subject's hand. If rather rigid standards are adopted for this technic, the results[8] agree well with those obtained by the Landis[9] direct micro-cannulation method in which the intubated nailfold skin capillary loops were used as the site for examination. Capillary blood-oxygen saturation was estimated oximetrically, using the spectroscopic technic,[4, 10] and again taking readings from the nailfold skin. Tissue edema was measured by a simple water-displacement plethysmograph attached to the terminal phalanx of the index finger. A Leitz incident-light capillary microscope was used to inspect the functional anatomy of the nailfold skin vasculature and note was taken of the morphology of the minute vessels,[11] as well as the dynamic changes in their tone, the occurrence of extravascular hemorrhages, etc. Arterial pressure was estimated routinely with a mercury sphygmomanometer.

Each of the above investigations was carried out kinetically and serially on both patients, (1) during the three-month pre-insulin observation period; (2) throughout the hypoglycemic episodes and continuing until consciousness was regained following the glucose interruption; (3) five hours post-insulin after the glucose interruption when the patients had fully recovered from their hypoglycemic experience.

In addition, spot checks were made of the blood

glucose levels,[12] both fasting during the initial baseline resting period and later at the clinical peaks of the insulin response. Similar observations were made of the blood specific gravity, using the Van Slyke and associates,[13] and Phillips et al.[14] copper sulphate falling drop method, to derive estimates of plasma protein, hemoglobin and hematocrit variation. Statistical significance was assayed by the analysis of variance technic and computation of the correlation ratio (eta^2), the latter providing a useful index of the extent to which the variation is dependent upon the individual monitor employed.

RESULTS AND DISCUSSION

These are displayed in the accompanying tables and figure. In every case in table 2 the mean values of the variable investigated are given for each of four phases of the patient's hypoglycemic experience and its interruption by glucose while, for comparison, similar mean values are displayed for the relevant pre- and post-insulin conditions.

Blood Flow in the Minute Vessels. Table 2 gives the changes found for corpuscular rate in the nailfold skin capillaries and probable cutaneous arteriolar flow as determined by skin temperature fluctuation respectively. Figure 1 illustrates graphically the corpuscular flow changes of the distal hairpin loops and focuses attention on the hypoxic implications of the coma state. Not only is cellular respiration impaired by depriving the cell of its glucose requirements; direct molecular oxygen delivery is also delayed. In Patient A (table 2) arteriolar blood flow inhibition follows precisely the pattern set by flow in the true capillaries, but in Patient B this is not so and the paradoxical rise in skin temperature at the deep coma phase, and at a time when corpuscular

FIG. 1. Mean capillary blood flow in Patient A (continuous line) and Patient B (dotted line). Ordinates: rate of flow (corpuscles per second); abscissa (reading from left to right): Pre-insulin baseline levels; pre-sopor state following insulin injection; hypoglycemic sopor; light coma; deep coma; initial response to 33.3 per cent glucose administration; "rebound" effect of absorbed glucose; later acute effects of glucose; "post-insulin" (levels obtained 5 hours following interruption of the hypoglycemic coma).

TABLE 1

Mean changes brought about by insulin in blood sugar, plasma protein, hematocrit and hemoglobin content

Time (fasting)	Blood sugar (mg. per cent) Patient A	Blood sugar (mg. per cent) Patient B	Plasma protein (gm. per cent) Patient A	Plasma protein (gm. per cent) Patient B*	Hematocrit (per cent) Patient A	Hematocrit (per cent) Patient B*	Hemoglobin (gm. per cent) Patient A	Hemoglobin (gm. per cent) Patient B*
Pre-insulin	85.000 (s=12.5) (N=4)	69.000 (s=6.5) (N=3)	8.047 (s=.4) (N=25)		46.591 (s=1.6) (N=23)		15.817 (s=.5) (N=23)	
Insulin			7.797 (s=.3) (N=30)	7.923	47.900 (s=2.3) (N=28)	48.805	16.282 (s=.8) (N=28)	16.579
Sopor	28.625 (s=9.1) (N=8)	30.556 (s=10.2) (N=9)						
Coma	23.125 (s=8.5) (N=16)	23.333 (s=12.1) (N=12)						
Difference			−0.250		+1.345		+0.465	
t test			5.124		4.854		4.927	
d.f.			53		49		49	
P			<.001		<.001		<.001	

*No specific gravities were available on the pre-insulin blood in the case of Patient B.

TABLE 2

Effect of various stages of hypoglycemia on capillary vascular variables and finger volume

Status		Capillary blood flow (corpuscles/sec.)		Skin temperature (°F)		Capillary blood pressure (mm.Hg)		Arterial pulse pressure (mm.Hg)	
		Patient		Patient		Patient		Patient	
		A	B	A	B	A	B	A	B
Pre-insulin	Mean	6.00	12.32	91.84	95.36	41.92	43.03	35.86	30.56
	s	7.3	13.3	3.7	1.6	12.9	13.1	11.8	6.7
	N	190	93	59	29	198	95	35	14
Pre-sopor	Mean	9.20	13.83	93.83	93.66	40.47	28.40	80.00	57.50
	s	1.9	8.4	1.6	1.2	14.6	8.4	8.2	12.6
	N	5	6	13	19	17	10	7	4
Sopor	Mean	4.97	16.92	90.84	91.36	21.93	21.58	96.74	60.00
	s	3.4	8.8	1.9	1.7	12.8	6.7	28.5	7.3
	N	29	13	38	24	40	19	43	28
Light coma	Mean	3.97	6.29	89.00	88.15	40.26	50.00	105.83	60.00
	s	4.2	6.5	1.4	3.4	24.4	0	19.7	18.7
	N	38	7	11	6	19	3	12	5
Deep coma	Mean	2.10	3.29	87.05	93.24	54.00	—	103.33	62.00
	s	2.2	5.3	1.4	0.5	8.9	—	40.8	16.4
	N	42	7	12	5	5	—	6	5
Early glucose	Mean	6.34	17.00	88.38	90.45	37.13	27.50	83.68	57.14
	s	8.3	14.8	4.3	3.8	35.5	7.5	15.7	13.8
	N	32	8	25	21	23	8	19	7
Rebound glucose	Mean	9.36	21.33	88.07	91.27	18.61	18.18	66.09	43.00
	s	8.8	13.4	4.7	3.0	5.1	1.4	18.0	16.4
	N	33	9	26	21	23	11	23	10
Late glucose	Mean	6.59	13.33	84.42	88.25	26.11	34.00	56.43	45.00
	s	6.5	6.2	5.4	2.9	13.1	4.9	10.1	11.9
	N	29	6	25	11	19	4	14	8
Post-insulin	Mean	13.43	24.39	93.27	94.40	34.25	35.11	44.32	39.46
	s	9.5	15.2	2.7	1.8	12.7	12.7	8.2	8.2
	N	131	101	32	52	143	92	37	28
F ratio		16.029	6.651	17.937	21.381	14.593	10.794	49.396	18.717
d.f.		8/520	8/241	8/232	8/179	8/478	7/234	8/187	8/100
n^2		.198	.181	.382	.489	.196	.227	.679	.600
P		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

motion in the capillaries is almost at a standstill, suggests the operation of a shunt mechanism which bypasses these vessels in this patient. If such were the case, a similar anomaly might be expected in the blood-oxygen saturation of the minute vessels in Patient B and table 2 lends support to this assumption.

Intravascular Pressures. Table 2 also compares the capillary blood pressure and arterial pulse pressure variations during insulin hypoglycemia. The resting pressures of both patients are characteristic of those found in schizophrenia,[8, 15] and only approximate healthy values under the influence of the glucose interruption. Progressive hypoglycemia would seem to influence capillary pressure in a biphasic fashion, a trough at the sopor stage being given by both patients. This dip is not seen to disturb the steady widening of the pulse pressures although the extent of this change is less evident in Patient B than in Patient A.

Tissue Volume and Other Changes. Digital tissue waterlogging is suggested in table 2 as occurring sequentially with deepening coma and raises the question of its source. Relative oxygen-lack increases capillary permeability to plasma,[16, 17] and even to whole blood.[18] According to Starling's hypothesis, the colloid osmotic pressure of the plasma proteins nicely balances the hydrostatic pressure within the capillary blood vessels. The increase in capillary pressures in insulin coma (table 2) would thus favor extravasation of fluid into the tissues in a fashion identical to its occurrence at rest in the schizophrenic process itself.[8] Further confirmation of these mechanisms was given by the falling plasma protein and rise in hematocrit and hemoglobin values (table 1) and by the microscopic observations on capillary tone made during the investigation reported here. Characteristic of these was primarily their changeableness. In both patients deepening hypoglycemia was accompanied by rapid alterations of capillary tone from extremes of vasoconstriction to similar vasodilatation, circumstances suggesting an intermittent facilitation of fluid transudation at least in the acral site of examination.

Blood O_2 saturation				Plethysmography (ccH_2O)	
R.S.	per cent	R.S.	per cent		
Patient				Patient	
A		B		A	B
24.9	(92)	22.2	(91)	4.68	4.78
11.2		11.9		0.5	0.3
331		128		35	8
19.0	(90)	21.1	(91)	4.34	4.63
4.2		5.5		0.4	0.3
2		9		7	4
15.6	(89)	17.1	(90)	4.53	4.99
4.2		5.1		0.4	0.2
34		21		16	8
15.3	(89)	15.8	(89)	5.17	4.86
5.9		4.1		0.6	0.2
42		28		3	5
9.7	(87)	15.8	(89)	5.25	5.50
2.5		3.0		0.5	0
21		27		6	2
20.1	(91)	20.3	(91)	4.48	4.50
6.8		6.7		0.6	0.4
45		15		8	6
34.4	(95)	35.6	(95)	4.22	5.00
8.7		8.3		0.3	1.1
44		36		11	4
26.4	(93)	26.2	(93)	4.44	—
5.6		7.9		0.5	—
22		31		5	—
29.3	(93)	26.7	(93)	4.32	4.23
9.9		7.8		0.4	0.5
244		156		40	27
28.305		28.346		4.820	4.965
8/777		8/442		8/122	7/56
.226		.383		.240	.381
<.001		<.001		<.001	<.001

SUMMARY

1. The acute responses of two nondiabetic human subjects to massive doses of insulin five times weekly for a three-month period are reported in terms of changes occurring in the capillary vasculature.

2. It was found that corpuscular flow rates in the skin capillaries fell significantly and progressively as hypoglycemic coma developed. Speed was regained when glucose was given and the coma interrupted. Skin temperature variations roughly paralleled these changes and suggested a similar influence on arteriolar blood flow. An increase in finger volume with the onset of coma indicated a waterlogging of the tissues and accompanied a small but significant fall in capillary blood-oxygen saturation, a rise in capillary blood pressure, decreased plasma protein, a rise in hematocrit and in hemoglobin content, and some rather characteristic changes in the tone of the minute vessels as observed capillaroscopically.

3. The metabolic implications of these findings are discussed briefly.

SUMMARIO IN INTERLINGUA

Hypoglycemia Inducite per Doses Massive de Insulina e su Effectos Super le Physiologia del Vasos Capillar in Humanos

1. Es reportate le acute responsas de duo nondiabetic subjectos human a massive doses de insulina administrate cinque vices per septimana durante un periodo de tres menses. Le responsas esseva studiate in tanto que illos se manifestava in alterationes occurrente in le vasculatura capillar.

2. Esseva constatate que le fluxo corpuscular in le capillares cutanee se relentava significative e progressivemente como function del disveloppamento de coma hypoglycemic. Le fluxo se reaccelerava quando glucosa esseva administrate e le coma esseva interrumpite. Variationes del temperatura cutanee occurreva plus o minus parallelmente a iste alterationes, lo que indicava un simile influentia super le fluxo de sanguine arteriolar. Un augmento del volumine digital occurrente con le declaration del coma indicava un invasion aquose del histos e accompaniava un parve sed significative reduction del saturation oxygenic del sanguine capillar, un augmento del pressiones de sanguine capillar, decrescite nivellos de proteina plasmatic, un augmento del hematocrite e del contento de hemoglobina, e certe satis characteristic alterationes in le tono del minute vasos observate per medios capillaroscopic.

3. Es presentate un breve discussion del implicationes metabolic de iste constatationes.

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Hunger and Appetite

Physiologists, in studying the activities of the gastrointestinal system, have found it valuable to distinguish between hunger and appetite. Hunger may be recognized by two components. The first is a generalized weakness which may be related to sensory nerve impulses from the alimentary canal, and perhaps occasionally to lowered blood sugar.[1, 2]

The second component is a more definite perception in the epigastric region, consisting of intermittent sensations of tension or pressure of brief duration. These hunger pangs are usually associated with appetite but may be independent of it. The physiological basis for hunger contractions appears to be inherited with relatively little modification from the experiences of the individual. These contractions have a fixed pattern (thirty minutes activity with one and a half to two hours rest) which does not vary markedly whether the period of abstinence from food is prolonged or short. A starving man will become weaker but not more uncomfortable. It is said that a man can live without food for five weeks but cannot survive lack of water more than five to ten days. Hunger of this type is stopped by solids in the stomach even though they may not be highly nourishing. The mechanism of the hunger contractions is not clearly understood. They are not dependent upon the extrinsic motor nerves, because they are evident even after these nerves to the stomach are cut. Blood sugar level may be a factor but contractions may occur while the contents of the last meal are still in the stomach.

Appetite, while often accompanying hunger, may be present without it. One may want to continue eating an excellent meal long after hunger has been satisfied. The components for appetite are principally psychological and are the result of the past experiences of the individual. We learn to like and dislike foods from our earliest days, and often these patterns are thoroughly fixed in adult life. The nature of the memories associated with the early ingestion of food will determine preferences in a manner independent of logical considerations, and hence will be puzzling to the physician who is attempting a rational therapy for a patient with nutritional problems. If we remember the old adage about there being no disputing matters of taste, or the wide variations in diet among the various nations of the earth, it will be easier to tolerate the food vagaries of our patients.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "The Psychology of Appetite"

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The Intestinal Tract in Diabetic Diarrhea
A Pathologic Study

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Although many of the gastrointestinal disturbances that occur in diabetic patients are unrelated to the diabetes or result from acute changes in fluid or electrolyte metabolism, certain other disturbances have been ascribed to degenerative complications of diabetes mellitus. Thus, in 1936 Bargen, Bollman and Kepler[1] described the syndrome "diarrhea of diabetes," in which unexplained diarrhea characterized by numerous watery stools and by urgency and tenesmus on defecation is associated with severe diabetes mellitus. Subsequent reports have emphasized the association of diabetic neuropathy with this disorder, and a neurogenic basis for the diarrhea has been proposed.

In a series of 125 cases of diabetic neuropathy, Rundles[16] noted that twenty-seven patients had an associated watery diarrhea, characterized in some by nocturnal exacerbations and fecal incontinence. Forty diabetic patients with intermittent nocturnal diarrhea were reported on by Sheridan and Bailey[18] in 1946. The average age of the patients in this group was forty-two years, with a range of 20 to 79 years; the diabetes, which had been poorly controlled, averaged nine years in duration. Symptoms of diabetic neuropathy had preceded the onset of diarrhea in twenty-three instances. Hodges, Rundles and Hanelin,[9] in a roentgenologic study of the gastrointestinal tract in thirty-five patients with diabetic neuropathy and associated gastrointestinal symptoms, found gastric retention and a delay in transit with segmentation of the barium column within the small intestine similar to the changes observed in patients following vagotomy. Roentgenologic abnormalities in the cases with severe constipation were surprisingly similar in type and degree to those noted in the presence of chronic diarrhea. In a study of the function of the peripheral vasomotor and sudomotor nerves in diabetic patients, Martin[13] noted that of two patients with associated nocturnal diarrhea, one exhibited a lack of peripheral vasoconstriction in response to cooling. Odel, Roth and Keating[15] reported the presence of gastrointestinal disturbance in 14 of 40 patients in whom diabetic autonomic neuropathy simulated the effect of surgical sympathectomy. Diarrhea and steatorrhea follow postganglionic sympathetic denervation of the intestinal tract in experimental animals.[6] Parasympathetic denervation of the intestine by means of vagotomy has also occasionally been followed by diarrhea in both man[19] and experimental animals.[5] The frequent observation of orthostatic hypotension, abnormalities of skin temperature and sweating, impotence, neurogenic vesical dysfunction and abnormal pupillary reactions in patients with diabetic diarrhea, has provided evidence of coexistent widespread autonomic neuropathy and has given support to the concept of a neurogenic basis for the disorder.[2]

While emphasizing the tendency of diabetes to cause disturbance in the function of autonomic nerves, Rundles[17] added, "While we are not lacking in confidence as to the validity of our functional studies and interpretations, we must admit that the morphologic aspects of the disease have received only fragmentary study." A review of the literature confirms the truth of this statement as it might apply to diabetic diarrhea. We have found no reports of detailed pathologic studies of the intestine in cases of diabetes, either in the presence or in the absence of diabetic diarrhea. The present report concerns such a study.

MATERIAL AND METHODS

Three groups of cases were selected from necropsy material in the Section of Pathologic Anatomy of the

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Mayo Clinic. Group I, composed of eight cases in which there had been clinical evidence of diabetic diarrhea, was selected by a careful study of the records of 351 diabetic patients who had died during the ten-year period immediately prior to January, 1954. Group II, selected from the same source of material, was made up of sixteen diabetic patients without a history of significant gastrointestinal symptoms but comparable in age and in duration of diabetes to the cases in group I. Group III contained ten nondiabetic patients without gastrointestinal symptoms, comparable in age to the other two groups. The ages, duration of diabetes, and causes of death of all thirty-four patients are listed in table 1.

The gross specimens of intestine were examined, and blocks of tissue, identified as precisely as possible with respect to segment of small or large intestine represented, were prepared for histologic study in an identical manner for all cases in the three groups. Formalin-fixed tissue imbedded in paraffin blocks was cut perpendicular to the surface of the bowel wall; serial sections of eight microns thickness were stained with hematoxylin and eosin, van Gieson connective tissue stain, cresyl violet and modified Bodian silver stain.

TABLE 1

Age, duration of diabetes and cause of death of all patients

	Case	Age, years	Duration of diabetes, years	Major cause of death
Group I Diabetic diarrhea	1	65	17	Coronary insufficiency; congestive heart failure
	2	31	13	Indeterminate coma
	3	72	25	Myocardial infarction
	4	60	15	Myocardial infarction
	5	66	8	Hypertension; congestive heart failure
	6	65	14	Bronchopneumonia
	7	49	14	Congestive heart failure
	8	18	16	Indeterminate coma
	Average	53	15	
Group II Diabetes without diarrhea	9	74	4	Rupture of heart
	10	77	15	Pulmonary embolism
	11	68	12	Suppurative myocarditis
	12	47	21	K-W;* uremia
	13	43	30	Myocardial infarction
	14	36	24	Myocardial infarction
	15	39	25	K-W; uremia
	16	34	19	Myocardial infarction
	17	26	22	K-W; congestive heart failure
	18	22	13	K-W; uremia
	19	24	6	Brain abscess
	20	28	25	K-W; uremia
	21	68	16	Coronary insufficiency
	22	60	15	K-W; uremia
	23	77	11	Rheumatic carditis; cerebral emboli
	24	42	20	K-W; uremia
	Average	48	17	
Group III Nondiabetic controls	25	13	–	Accidental
	26	37	–	Congestive heart failure
	27	38	–	Brain tumor
	28	57	–	Renal insufficiency
	29	58	–	Brain tumor
	30	62	–	Brain tumor
	31	64	–	Coronary sclerosis
	32	61	–	Coronary insufficiency
	33	79	–	Subdural hematoma
	34	84	–	Congestive heart failure
	Average	55	–	

*K-W=Kimmelstiel-Wilson intercapillary glomerulosclerosis.

Five hundred and eighty slides were prepared from 111 segments of intestine.

The mucosa was evaluated with special attention to possible atrophy, inflammation or ulceration. The muscular coats were studied with respect to general appearance on both hematoxylin and eosin and the van Gieson-stained material. The status of the blood vessels in all layers of the bowel wall was noted in the same sections. The intrinsic nerve structures of the intestine were studied on all of the slides. The morphology of all ganglion cells in the plexuses of Auerbach and Meissner was evaluated in the preparations stained with hematoxylin and eosin and with cresyl violet. Abnormalities noted were classified as chromatolysis, manifested by swelling, degranulation, and variations in staining properties of the cytoplasm; pyknosis, characterized by shrinking of the cells; or as vacuolization of the cytoplasm. The amount of connective tissue associated with the ganglia was noted in sections prepared with van Gieson stain. An attempt was made to evaluate the status of the nerve fibers within and between the ganglia of the sections prepared with the modified Bodian stain. Quantitation of the ganglia in the enteric plexuses was not possible, because circumferential sections of the intestine were not available in most instances. Since the specimens varied greatly in degree of distention at the time of fixation, valid comparative counts could not be made on the available material. Furthermore, studies on laboratory animals have demonstrated wide variations in the number of ganglia in different segments of the intestinal tract;[11, 12] the establishment of adequate normal values in the human was not within the scope of this study. Extrinsic autonomic ganglia and nerve fibers were not available for study.

RESULTS AND COMMENT

Although the study was concerned primarily with the pathologic findings in the intestine in diabetes, a detailed review of the clinical data of the cases with diabetic diarrhea was made for correlative reasons. Such a review not only furnished evidence of other diabetic complications that might have had an effect on intestinal function, but documented the diagnosis of diabetic diarrhea as well. One or more of the salient features of diabetic diarrhea, namely, nocturnal exacerbation, fecal incontinence, or intermittency, was present in all cases. No case was included in this study if there was clinical or pathologic evidence of any condition other than diabetes which could have caused the diarrhea. In none was there pathologic evidence suggesting external pancreatic insufficiency. In case 7, one of three stool examinations had exhibited excessive fecal fat; however, administration of pancreatin in therapeutic amounts had not improved the diarrhea. This combination of severe diabetes mellitus and steatorrhea in the absence of external pancreatic insufficiency has been reported previously.[2]

The clinical data with respect to the diabetes and its complications for the eight cases of diabetic diarrhea are listed in table 2. The mean age of these eight patients was fifty-three years with a range of 18 to 72 years. The average duration of diabetes at death was fifteen years, and the average duration at the onset of diarrhea was eight years. The diabetes was severe enough to necessitate the use of insulin, in addition to diet, in all cases; and control of the diabetes had been poor in at least five of the cases, as evidenced by coma, frequent insulin reactions or the lack of urine testing for sugar. There was a strikingly high incidence of degenerative complications of diabetes, including retinopathy, nephropathy and neuropathy (table 2).

In only three of the eight cases of diabetic diarrhea were gross abnormalities of the intestine noted at the time of necropsy. The findings recorded were thickening of the wall of the jejunum and the presence of a Meckel diverticulum in case 4, pedunculated polyps in the transverse and sigmoid colon in case 5, and four small ulcers in the low rectum in case 8.

With the exception of the foregoing lesions, no significant histologic abnormalities were noted in the mucosa. The only abnormality noted in the musculature of the bowel was the presence of excessive connective tissue within the longitudinal muscle coat in two cases of group I. The outer muscle layer in one section of jejunum from case 4 was almost completely replaced by fibrous connective tissue. Although another section of jejunum from the same case exhibited only minimal fibrosis, a section of ileum was moderately involved by the same process. The only other instance of similar fibrosis was in a section of colon in case 1.

Vascular lesions in the intestine were not striking in any of the cases. There was no evidence of arteriolar degeneration in association with the fibrotic muscle layer. Moderate thickening of the walls and narrowing of the lumina of several arterioles in the submucosa were noted in sections of duodenum in case 4, jejunum in cases 5 and 6 and ileum in cases 2, 20 and 26. Similar arteriolar sclerosis was present in the serosa of the ileum in case 4 and of the colon in case 6. Slight medial or subintimal thickening of the small arteries in the submucosa was found in the colon in case 6 and in

TABLE 2
Clinical data relating to cases with diabetic diarrhea

	Case							
	1	2	3	4	5	6	7	8
Age at time of death, years	65	31	72	60	66	65	49	18
Total duration of diabetes, years	17	13	25	15	8	14	14	16
Duration of diarrhea, years	4	6	20	4	1*	1	10	6
Severity of diabetes, grade†	4	4	3	3	3	3	3	4
Complications of diabetes‡								
Retinopathy	+	+	+	−	+	+	+	+
Nephropathy								
Albuminuria (grade, basis 4)	0	−	0	0	2	3	4	3
Blood urea, mg. per 100 cc.	−	68	50; 94	28	62; 143	−	86; 120	76; 200
Neuropathy								
Diminished muscle stretch reflexes	+	+	+	0	+	+	−	+
Diminished cutaneous sensation	−	+	+	0	−	−	−	+
Vesical dysfunction	0	+	−	0	0	+	−	−
Diminished pupillary reflexes	−	+	−	±	+	−	+	+

*Intermittent diarrhea lasting for one year, followed by intractable constipation for three years prior to death.
†Grade 3 indicates insulin dosage of 30 units or less daily; grade 4 indicates that more than 30 units of insulin were required daily.
‡Plus sign indicates finding present; ± indicates finding doubtful; 0 indicates normal finding; − indicates no data.

the duodenum and ileum in case 30. Since the vascular lesions were neither limited to diabetic patients nor universally present in cases with diabetic diarrhea, their role in the pathogenesis of intestinal dysfunction is doubtful.

A tabulation of the morphologic abnormalities noted in the enteric ganglion cells in all three groups is given in table 3. The incidence of pyknosis, chromatolysis and vacuolization is expressed as the number of specimens from each case in which ganglia exhibited the particular change. The total number of specimens so altered in each group is expressed as a percentage of all specimens in that group. The marked similarity in the incidence of chromatolysis and of vacuolization in ganglion cells of Auerbach's plexus in all three groups is striking. Although abnormalities were noted in the cells of Meissner's plexus with much less frequency, the incidence in the three groups was again quite similar. The infrequency with which changes were noted in the submucous plexus is probably due, at least in part, to the relative paucity of ganglion cells in this plexus as compared with the myenteric plexus of Auerbach.[14] Although it was not possible to quantitate precisely the abnormalities within the individual ganglia of the sections in each group, the extent was not appreciably different in any of the groups of cases. Significant hyperpigmentation was not observed in any ganglion cells.

The ganglia in both Auerbach's and Meissner's plexuses lie within the stroma of the intestinal wall. In addition to the fibrous tissue in this stroma which surrounds the ganglia, the supporting cells within the ganglia are felt by some investigators to be of connective tissue rather than of neural origin.[4, 8, 12] Fibers that stained with van Gieson connective tissue stain were noted around all of the ganglia and frequently among the groups of neurons. In one section of ileum in case 1, one section of jejunum in case 4, in the jejunum in case 11 and in the ileum in case 30, the fibrous tissue surrounding the ganglia of Auerbach's plexus was unusually prominent. The adjacent blood vessels did not appear abnormal.

Because of technical difficulties encountered with the use of the modified Bodian stain, the evaluation of the nerve fibers in the enteric ganglia was not possible in the majority of the specimens. It seems significant, however, that in thirty-two specimens histologically intact nerve fibers or ganglion cell processes were noted in association with ganglia that appeared abnormal with respect to either pyknosis, chromatolysis, vacuolization or combinations thereof. This finding, in addition to the presence of morphologic abnormalities in the neurons irrespective of previous dysfunction of the intestines, suggests that the morphologic changes either were the result of nonspecific functional alterations in the neurons,[10] possibly related to the terminal illness,[7, 12] or were due to postmortem autolysis and fixation artifact.[8] Abnormalities of ganglion cells in case 25, in which the patient was a thirteen-year-old boy who died very suddenly of accidental causes, support the latter concept.

In view of the lack of correlation between intestinal dysfunction and changes in the neurons in the enteric ganglia, which are apparently solely related to parasympathetic innervation,[8] and because of the marked tech-

TABLE 3

Pathologic study of the intestinal tract in diabetes mellitus: Histologic abnormalities of ganglion cells in plexuses of Auerbach and Meissner*

	Case	Number of specimens†	Pyknosis		Chromatolysis		Vacuolization	
			A‡	M‡	A	M	A	M
Group I	1	6	1	0	6	0	3	0
Diabetic diarrhea	2	8	0	0	5	2	2	0
	3	5	0	0	4	1	4	1
	4	5	1	0	5	1	3	2
	5	2	0	0	2	1	0	0
	6	2	0	0	2	0	2	1
	7	10	0	0	9	2	5	2
	8	3	0	0	3	0	3	1
Total		41	2	0	36	7	22	7
Per cent of specimens			5	0	88	17	54	17
Group II	9	5	1	0	4	0	5	2
Diabetes without	10	3	1	0	3	0	1	0
diarrhea	11	3	0	0	2	0	2	0
	12	3	0	0	2	0	3	1
	13	3	0	0	3	1	1	0
	14	2	0	0	2	0	1	0
	15	2	0	0	2	0	1	0
	16	2	0	0	2	1	0	0
	17	2	1	0	2	0	0	0
	18	3	2	0	3	0	2	0
	19	3	0	0	2	1	2	1
	20	5	0	0	5	3	4	1
	21	3	1	0	2	0	2	0
	22	2	0	0	2	0	1	0
	23	3	0	0	2	0	0	0
	24	2	0	0	0	0	0	0
Total		46	6	0	38	6	25	5
Per cent of specimens			13	0	83	13	54	11
Group III	25	6	0	0	4	1	1	0
Nondiabetic	26	5	0	0	5	0	5	0
controls	27	6	0	0	6	0	3	1
	28	5	0	0	4	2	4	0
	29	5	0	0	5	1	1	0
	30	7	1	0	5	2	5	1
	31	6	0	0	5	2	4	0
	32	5	0	0	4	0	3	0
	33	6	0	0	4	2	4	0
	34	5	0	0	4	0	4	1
Total		56	1	0	46	10	34	3
Per cent of specimens			2	0	82	18	61	5

*Expressed as number of specimens revealing abnormality. See text.
†Specimen indicates block of tissue from which at least four slides were examined.
‡A=myenteric plexus of Auerbach. M=submucous plexus of Meissner.

nical limitations in the evaluation of the small sympathetic nerve fibers of the intestine with the methods that are available for use on fixed tissue,[12, 17] the neurogenic basis of diabetic diarrhea has not received direct pathologic confirmation from this study. The lack of pathologic evidence favoring any other etiology, however, may provide indirect evidence supporting this concept.

SUMMARY

Diarrhea characterized by an intermittent course, nocturnal exacerbations and fecal incontinence has been observed in association with diabetes mellitus and has been ascribed by many investigators to the effects of autonomic neuropathy on the motor function of the intestinal tract. However, pathologic evidence supporting this or other etiologic mechanisms has not been presented.

The present report concerns a gross and microscopic study of the small and large intestine in eight necropsy cases of diabetic diarrhea, sixteen diabetic cases without diarrhea and ten nondiabetic cases. Specimens were carefully evaluated with respect to possible alterations in mucosa, muscularis, blood vessels and autonomic nerve structures. In no instance was there gross evidence of disease involving the intestinal tract which could have caused the diarrhea. No significant difference was noted in the incidence of mucosal, muscular

or vascular abnormalities in the three groups of cases. Chromatolysis, pyknosis and vacuolization of the autonomic ganglion cells were also noted with comparable frequency in all three groups and were felt to represent nonspecific changes, due to postmortem autolysis or fixation artifact. This study did not, therefore, provide pathologic confirmation of the neurogenic basis of diabetic diarrhea, although absence of other pathologic changes of etiologic importance may have offered indirect support to such a concept.

SUMMARIO IN INTERLINGUA

Le Via Intestinal in Diabete Mellite, con Referentias Special a Diarrhea Diabetic: Un Studio Pathologic

Diarrhea characterisate per un curso intermittente, exacerbationes nocturne, e incontinentia fecal ha essite observate in association con diabete mellite, e multe investigatores lo ha ascribite al effectos de un neuropathia autonome super le function motori del via intestinal. Tamen, nulle datos pathologic ha essite presentate que supporta iste o ulle altere conception del mechanismo etiologic.

Le presente reporto concerne le studio grossier e microscopic del intestinos tenue e crasse in octo casos necropsiate de diarrhea diabetic, dece-sex casos diabetic sin diarrhea, e dece casos nondiabetic. Le specimens esseva cautemente evalutate in re possibile alterationes del mucosa, del strato muscular, del vasos sanguinee, e del structuras de nervo autonome. Nulle caso exhibiva signos grossier de morbo involvente le via intestinal e capace a causar le diarrhea. Nulle differentias significative esseva notate in le presentia de anormalitates mucosal, muscular, o vascular inter le tres gruppos de casos studiate. Chromatolyse, pyknosis, e vacuolisation del cellulas autonomo-ganglionic esseva etiam notate con comparabile grados de frequentia in omne le tres gruppos. Illos esseva interpretate como representantes de alterationes nonspecific debite a autolyse post morte o a artefactos de fixation. Assi iste studio non produceva un confirmation pathologic del base neurogenic de diarrhea diabetic, ben que le absentia de altere constatationes pathologic de importantia etiologic pote esser interpretate como un supporto indirecte de ille conception.

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Primary Optic Atrophy in Diabetes Mellitus

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In the late nineteenth century, publications on ocular complications of diabetes mellitus frequently mentioned primary optic atrophy. Clifford Allbutt in 1871 stated "atrophy of the optic discs . . . does undoubtedly occur in a sufficient number of cases of glycosuria to make the coexistence seem more than accidental." In 1875 Leber quoted a number of cases recorded by other observers, but stated that he had not seen such a patient himself. In the 1927 edition of von Noorden's book on diabetes, 4 per cent of 477 diabetic patients are recorded as suffering from simple optic atrophy. More recently, Waite and Beetham (1935) found optic atrophy in 0.6 per cent of 2,002 diabetics and in 0.4 per cent of 457 nondiabetics. The only other reference in recent literature is that of Wolfram (1938) who reported from the Mayo Clinic four cases of diabetes mellitus and simple optic atrophy among siblings. This communication is concerned with two further cases.

REPORT OF CASES

The two patients were siblings and there was no family history of diabetes mellitus or poor vision.

Case 1. H. M., a male, age 34, developed the classical symptoms of diabetes mellitus at age of 12. In 1943, twelve years later, the patient complained of failing vision. The fields were normal and there was no central scotoma. Vision was recorded as 0.3 in both eyes and there was a bilateral optic atrophy of the primary type. During the next year vision deteriorated to 0.1 in both eyes; the patient was thought to have a "chiasmatic arachnoiditis" since the macular appeared unaltered.

At the age of 25 patient complained of pain in the left chest, cough with sputum and a rapid loss of weight. Sputum was positive for tubercle bacillus and there were bilateral changes of bronchopneumonia on x ray of the chest. He was admitted to a sanatorium and after three months noted some deafness. He had not received streptomycin. Hearing gradually deteriorated until he had to be fitted with a hearing aid.

This patient's diabetic control has always been difficult and he is still a very unstable diabetic whose weight fluctuates from 126—140 lb. Physical examination shows no enlargement of the heart and the peripheral and retinal vessels are normal. B.P. 130/80. Electrocardiogram shows no abnormality. The thoracoplasty performed in October 1953 is very satisfactory and sputum is consistently negative for tubercle bacilli. Repeated x rays of chest confirm the satisfactory state of the thoracoplasty and also a healed lesion in the right upper zone. No abnormal viscus was palpated in the abdomen. Urinalysis was negative repeatedly for albumin.

Physical examination is negative apart from the bilateral optic atrophy associated with complete blindness and the audiograph showing complete absence of bone conduction to all frequencies. Although the patient complains of a lurching, drunken gait a complete neurological examination shows no abnormality. For example there was no lateral nystagmus, no twitching facial muscle. There were no tremors of the tongue and no wasting of any muscles. Muscle power and tone were good and no contractures were evident. Reflexes were present and brisk, the plantar response being flexor. All sensation was normal and there was no static ataxia.

The hemoglobin was 94 per cent (13.6 gm. per 100 ml.), total plasma cholesterol 182 mg. per 100 ml. Plasma proteins were normal and E.S.R. was 7 mm. in first hour.

The present diabetic control is unsatisfactory on 170 gm. of carbohydrate and 68 units of insulin a day as a 4:3 mixture of amorphous:crystalline insulin zinc suspension.

Case 2. B. M., a female, age 30, started diabetes mellitus at the age of 7. There were no complications and although the patient was emotionally unstable she progressed satisfactorily on a diet of 110 gm. carbohydrate and two doses of regular insulin, 24 units morning and night.

Eleven years later, in 1943, the patient complained of failing vision. At this time the visual fields were normal and there was no central scotoma. Vision was recorded as 0.5 in both eyes. The patient had a definite primary optic atrophy and at this time was considered to have a tremor of the right hand and bilateral slight ptosis. The ocular movements were thought to be defective in range.

A further ten years elapsed with no new complications, until 1953 when the patient noted an increasing deafness, tinnitus in the left ear, attacks of throbbing headache and a sensation of "everything falling out."

The present condition reveals a reasonably stable diabetic patient whose weight is steady. Physical examination shows no enlargement of the heart, although the diastolic blood pressure is consistently raised: B.P. 140/90. The electrocardiograph is normal. There are no abnormal physical findings in the respiratory system and an x ray of the chest is normal. Although the patient experiences intermittent amenorrhea no abnormal physical signs are elicited in the abdomen nor in the pelvis. There is no albuminuria.

Physical examination is otherwise normal apart from the bilateral optic atrophy and an audiograph showing complete absence of bone conduction to all frequencies. No other abnormal findings were elicited in a complete neurological

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examination similar to the one performed on Case 1. The hemoglobin was 95 per cent (13.8 gm. per 100 ml.), R.B.C. 4,400,000, E.S.R. 13 mm. in the first hour, W.B.C. 9,300, with a normal differential count.

The present diabetic control is not satisfactory on 160 gm. carbohydrate and 40 units of insulin a day as 1:3 mixture of amorphous:crystalline insulin zinc suspension.

DISCUSSION

Efforts were made to find some causal relationship between the diabetes and the optic atrophy in both patients. The blood Wassermann reaction was negative and radiographs of the skull showed a normal sella in each case. Audiographs were identical and showed no bone conduction to all frequencies. The electroencephalograms showed no definite abnormality, either when at rest or during overbreathing.

Social status of the family was poor and diet far from ideal, but there appeared to be no evidence of malnutrition nor avitaminosis in other family members.

The mother complained of defective vision. There was, however, no evidence of optic atrophy. The father died of chronic bronchitis and cardiac failure, with no evidence of defective vision. The two patients presented in this report are brother and sister. The male is the eldest of three children. A second child, two years younger, another male, is apparently healthy. Certainly there is no evidence of frank diabetes nor defective vision nor defective hearing. The female patient is the youngest child. There is no evidence in other members of the family of diabetes, blindness, nor deafness.

Sir Geoffrey Jefferson of Manchester, having seen the first patient previously, saw the girl in 1944. He reported that "The brother having optic atrophy suggests Leber's primary optic atrophy, as does the age incidence, though a sex-linked inheritance is absent." After considering the possibilities he believed that Leber's disease was on the whole the most likely diagnosis.

Wagener, in discussing the four patients, presented at the Mayo Clinic by Wolfram (1938), states that chronic retrobulbar neuritis is the most frequent lesion of the optic nerve associated with diabetes mellitus. In these four cases, however, there was no central scotoma. He stated that the gradual onset of visual loss and its steady progression did not justify the diagnosis of the common familial optic atrophy, Leber's disease. This, he considered, usually appears as an acute retrobulbar neuritis with a tendency to partial recovery. He thought the lesion in each of these four children to be a bilateral progressive primary optic atrophy. Wagener (1955) in a personal communication has stated that three of Wolfram's patients had subnormal hearing as tested for a watch tick. Furthermore two of these children were re-examined after 11 years and during this interval optic atrophy had progressed to the stage of almost complete blindness. Wagener (1955) also informs us that two of the patients have developed a cord bladder after 11 years. This lesion is considered to be part of a myelopathy. The cases reported here had suffered diabetes mellitus for 24 and 22 years respectively. There is no evidence of a myelopathy at present.

Ludo von Bogaert (1955) states, "It is well known that the more complex a hero-degenerative affection is anatomically, the more points of contact it has with other groups." When there is enough well studied material, a statistical analysis may allow geneticists to distinguish biotypes within the range of hereditary optic atrophy.

The similarity between Wolfram's four patients and the two patients presented here is striking. We consider that the patients of both series fall within the range of the hereditary primary optic atrophy.

SUMMARIO IN INTERLINGUA

Atrophia Optic Primari in Diabete Mellite

Es presentate le historia clinic de un fratre e un soror. Illes habeva suffrite de diabete mellite durante 24 e 22 annos respectivemente, e il habeva nulle indication de myelopathia. Ambes disveloppava atrophia optic primari, e le audiographo demonstrava subsequentemente un complete absentia de conduction ossee a omne frequentias. Il existe un frappante similitude inter quatro patientes presentate al Clinica Mayo in 1938 e le duo patientes discutite in iste articulo. Es exprimite le opinion que le patientes in ambe casos debe esser considerate como exemplos de hereditari atrophia optic primari.

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A Multi-interval Blood Glucose Method Utilizing the Clinitron

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The Wilkerson-Heftmann rapid blood sugar screening test[1] was originally devised for large-scale diabetes detection programs. However, this test would be next to worthless for mass screening for diabetes had it not been realized that some automatic mechanical device was needed to expedite the number of tests performed in any period. This led to the invention of the Clinitron‡ by Hewson (figure 1). With the Clinitron it is possible for a single attendant to process 4,300 Wilkerson-Heftmann blood sugar screening tests in forty hours. Wilkerson and Heftmann[1] found the test to be accurate within approximately 10 mg. per 100 ml., a fact confirmed by one of us (E.A.H.) previously[2] and again confirmed in the present study.

The modification of the Wilkerson-Heftmann test herein proposed extends the utility of the Clinitron beyond simple diabetes detection drives which are apt to be sporadic and, in some areas, too limited in scope to justify purchase of the machine.

The Clinitron is a machine which automatically delivers reagent tablets to test tubes containing blood-water mixture and rotates the test tubes over a critically timed heating element, thereby effecting the chemical changes necessary for the determination of levels of blood glucose present in the blood samples. The operator merely places the samples of blood diluted with water into the Clinitron. In about four minutes a color change in the reaction tube indicates whether the glucose concentration of the sample is above or below a designated value. Five or six test samples can be processed in approximately eight minutes, or about one-fifth the time required to process a blood sugar determination by conventional methods.

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‡The Clinitron is manufactured by the Mathewson Machine Works, Quincy, Massachusetts.

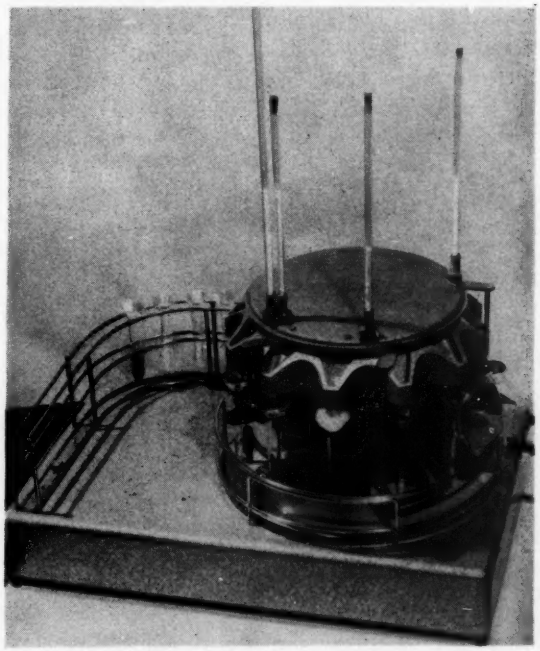

FIG. 1. Photograph of the Clinitron, an automatic device for mechanized processing of blood specimens. This instrument is necessary to perform the multi-interval blood glucose method.

The principal steps of procedure are as follows: Blood is deproteinized by boiling with zinc hydroxide (protein precipitation reagent tablets 1 and 2).* A fixed quantity of potassium ferricyanide in tablet form is added which, in the case of tablet 3A, will be completely reduced to potassium ferrocyanide by 0.13 mg. of glucose. Tablet 3B will be completely reduced by 0.18 mg. of glucose. If the blood glucose concentration is not high enough to reduce completely the potassium ferricyanide, any remaining will oxidize iodide to iodine in the acid medium containing tartaric acid created by tablet 4. The free iodine then turns the starch indicator

*Reagent tablets for the Wilkerson-Heftmann test are manufactured by Eli Lilly and Company, Indianapolis, Indiana.

blue. A colorless reaction indicates that no excess ferricyanide remains after boiling with blood glucose. The glucose concentration in the sample of blood therefore is greater than 0.13 mg. in the case of tablet 3A, or greater than 0.18 mg. in the case of tablet 3B.

Actual Mechanical Operation: One tenth ml. of blood is diluted with 5 ml. of water in a funnel-shaped test tube. This tube is automatically moved close to a continuous heating coil. When the tube reaches station 1, it trips a lever and releases one tablet of blood precipitation tablet No. 1 and one tablet No. 2. The fluid mixture begins to boil and, as the tube moves farther along the heating coil, steam is liberated and the precipitated proteins are forced up toward the funnel-shaped top of the tube to which they adhere.

As the tube is moved to station 3, it again trips a lever and a tablet of potassium ferricyanide is delivered.* Boiling continues at a somewhat reduced rate until the tube is immersed in a cooling bath at station 4. At this point a tablet of tartaric acid is delivered. The operator notes the color of the reaction tube after it emerges from the cooling chamber, completing the process.

The original purpose of the Clinitron was for screening blood sugars above and below 130 and 180 mg. per 100 ml. using 0.1 ml. of blood diluted in 5 ml. of water. However, by varying the volume of a given blood sample and keeping the concentration of potassium ferricyanide constant, almost any level of blood glucose concentration can be determined by a series of volume increments.

The experimental portion of this paper deals with a method of determining the accuracy and sensitivity of ferricyanide tablets 3A and 3B, and a method for determining blood glucose levels above and below 130 mg. per 100 ml. and above and below 180 mg. per 100 ml. by means of a simple dilution technic.

Experimental: The first object was to determine the accuracy and sensitivity of tablets 3A (130 mg. per 100 ml. level) and 3B (180 mg. per 100 ml. level). Blood samples of normal and diabetic patients were received from the Grand Forks Clinic. Potassium oxalate and sodium fluoride were used as anticoagulant and preservative respectively. The samples were placed in a refrigerator and analyzed for glucose content within forty-eight hours. Prior to being run in the Clinitron, samples were analyzed for glucose content by the method of Somogyi[3] and Nelson.[4]

Known volumes of blood were added to a series of reaction tubes, each containing 5 ml. of water, by means of small-bore calibrated pipettes and microburettes. These volumes containing specific quantities of glucose (previously determined by the Somogyi-Nelson technic), were processed by the Clinitron. By utilizing concentrations above, at the level of, and below that necessary for the ferricyanide tablets to react, a good approximation was made of the accuracy and duplication of reaction of the two types of tablets.

Tests of Tablet 3A: For testing tablet 3A (130 mg. per 100 ml. level) volumes of blood that contained 0.12, 0.13, and 0.14 mg. of glucose were added to 5 ml. of water in the Clinitron reaction tubes. We felt that an accuracy of ± 10 mg. per 100 ml. would be sufficient for a multi-interval blood glucose method.

If the reaction tube turned blue at the end of the run, this was taken to mean that the blood sample contained less than 0.13 mg. of glucose. If the reaction tube remained colorless, this was taken to mean that the blood sample contained more than 0.13 mg. of glucose. The amount of glucose in each of the blood samples was known, thus enabling us to check each reagent tablet by noting the concentration of glucose necessary to produce a change in color. This procedure was checked by a more sensitive technic of dilution. The error incurred in pipetting very small quantities of blood can be minimized by diluting the test blood tenfold with water, thus permitting a tenfold increase in volume to be pipetted. This is possible since the final volume of blood-water mixture in the reaction tube is not critical. The reaction proceeds equally well with from 3.0 to 6.0 ml. of water.

When blood specimens with low glucose concentration were used, it was found that there was no satisfactory agreement between the end-point indicated by the test tablet and the known concentration of glucose present in the sample. Further investigation showed that when more than 0.18 ml. of blood was added to the reaction tube, insufficient deproteinization occurred, as demonstrated with a quantitative biuret test. Thus, it was demonstrated that with the manufacturer's original procedure, the Clinitron did not function accurately when relatively large samples of blood were used. Adequate deproteinization was effected by simply adding one extra tablet of each reagent, 1 and 2, respectively. We therefore adopted the new procedure mentioned above which permitted us to use volumes of blood greater than 0.15 ml. The addition of another tablet of each reagent, 1 and 2, respectively, in no way affected the accuracy

*Only two reagent tablets of potassium ferricyanide are currently available, namely, reagent 3A, which screens at 130 mg. per 100 ml. level, and reagent 3B, which screens at 180 mg. per 100 ml. level.

of results, and actually improved the estimation of blood glucose concentrations in the 50-130 mg. per 100 ml. range by virtue of optimal deproteinization.

Test tablet 3B was checked in an identical manner, except that levels of 0.17, 0.18, and 0.19 mg. of glucose were used.

As the results in table 1 and 2 indicate, both tablets exhibited sufficient sensitivity to be utilized in the multi-interval blood glucose method herein proposed.

Multi-interval Method for Blood Glucose Levels above 130 mg. per 100 ml.: A series of five reaction tubes, each containing 4.0 ml. of distilled water, is prepared. One ml. of blood is diluted with 9.0 ml. of water in a separate test tube and mixed.

0.9 ml. of blood-water mixture is added to tube 1
0.8 ml. of blood-water mixture is added to tube 2
0.7 ml. of blood-water mixture is added to tube 3
0.6 ml. of blood-water mixture is added to tube 4
0.5 ml. of blood-water mixture is added to tube 5

Utilizing tablet 3A, the first tube in the series showing a blue reaction* is considered the end-point. A blue reaction in tube No. 1 represents a blood glucose level of less than 144 mg. per 100 ml., but more than 139 mg. per 100 ml. A blue reaction in tube No. 2 represents a value of less than 162 mg. per 100 ml., but more than 144 mg. per 100 ml. A blue reaction in tube No. 3 represents a value of less than 186 mg. per 100 ml., but more than 162 mg. per 100 ml. A blue reaction in tube No. 4 represents a value of less than 217 mg. per 100 ml., but more than 186 mg. per 100 ml. Finally a blue reaction in tube No. 5 represents a value of less than 260 mg. per 100 ml., but more than 217 mg. per 100 ml. Table 3 compares the results obtained from blood specimens analyzed for glucose content by both the Somogyi-Nelson technic and the Clinitron multi-interval blood glucose method using tablet 3A.

Utilizing tablet 3B in the identical procedure as given above, a blue reaction in tube No. 1 represents a glucose level less than 200 mg. per 100 ml. but more than 180 mg. per 100 ml., etc. Table 4 illustrates the results with tablets 3B in place of tablets 3A.

Thus, by utilizing both tablets 3A and 3B in this dilution method, it is possible to determine blood glucose levels in clinically practicable increments. The range can be further expanded by using a larger number of reaction tubes with smaller increments of blood.

*Infrequently, the end-point may be seen as a faint blue tinge, indicating a level of blood glucose nearly identical to that necessary to reduce the potassium ferricyanide totally.

TABLE 1
Results of evaluation of sensitivity of reagent tablet 3A

	Concentration	V_1	Reaction	V_2	Reaction	V_3	Reaction
1.	198	.60	B	.66	C	.71	C
2.	200	.60	B	.65	C	.70	C
3.	202	.59	B	.64	C	.69	C
4.	204	.59	B	.64	C	.69	C
5.	218	.55	B	.60	B	.64	C
6.	251	.48	B	.50	B	.56	C
7.	253	.47	B	.51	C	.55	C
8.	267	.45	B	.49	B	.52	C
9.	280	.43	B	.46	B	.50	C
10.	281	.43	B	.46	B	.50	C
11.	289	.42	B	.45	B	.48	C
12.	320	.38	B	.41	B	.44	C
13.	324	.37	B	.40	C	.43	C
14.	375	.32	B	.35	B	.37	C
15.	420	.29	B	.31	C	.33	C

Concentration=Actual blood glucose concentration in mg. per 100 ml. as determined by the Somogyi-Nelson technic.

V_1=That volume 1:10 dilution of blood and water containing 0.12 mg. of glucose.

V_2=That volume 1:10 dilution of blood and water containing 0.13 mg. of glucose.

V_3=That volume 1:10 dilution of blood and water containing 0.14 mg. of glucose.

Reaction=Color of reaction after completed run in the Clinitron where "C" means colorless, indicating a glucose concentration above 0.13 mg., and "B" means blue, indicating a glucose concentration below 0.13 mg.

TABLE 2
Results of evaluation of sensitivity of reagent tablet 3B

	Concentration	V_1	Reaction	V_2	Reaction	V_3	Reaction
1.	198	.86	B	.91	C	.96	C
2.	200	.85	B	.90	C	.95	C
3.	202	.84	B	.89	C	.94	C
4.	204	.83	B	.88	B	.93	C
5.	218	.78	B	.83	B	.87	C
6.	251	.68	B	.72	C	.76	C
7.	253	.67	B	.71	B	.75	C
8.	267	.64	B	.67	B	.71	C
9.	280	.61	B	.64	C	.68	C
10.	281	.60	B	.64	C	.68	C
11.	289	.59	B	.62	B	.66	C
12.	320	.53	B	.56	B	.60	C
13.	324	.52	B	.56	B	.59	C
14.	375	.45	B	.49	C	.51	C
15.	420	.40	B	.43	B	.45	C

Concentration=Actual blood glucose concentration in mg. per 100 ml. as determined by the Somogyi-Nelson technic.

V_1=That volume 1:10 dilution of blood and water containing 0.17 mg. of glucose.

V_2=That volume 1:10 dilution of blood and water containing 0.18 mg. of glucose.

V_3=That volume 1:10 dilution of blood and water containing 0.19 mg. of glucose.

Reaction=Color of reaction after completed run in the Clinitron where "C" means colorless, indicating a glucose concentration above 0.18 mg., and "B" means blue, indicating a glucose concentration below 0.18 mg.

TABLE 3

Comparison of results obtained from blood specimens analyzed for glucose content by the Somogyi-Nelson technic and the Clinitron multi-interval blood glucose method using tablet 3A

	Concentration	Tube 1	Tube 2	Tube 3	Tube 4	Tube 5
1.	130	B	B	B	B	B
2.	139	B	B	B	B	B
3.	156	C	B	B	B	B
4.	159	C	B	B	B	B
5.	160	C	B	B	B	B
6.	176	C	B	B	B	B
7.	178	C	C	B	B	B
8.	182	C	C	B	B	B
9.	198	C	C	B	B	B
10.	200	C	C	B	B	B
11.	204	C	C	C	B	B
12.	210	C	C	C	B	B
13.	216	C	C	C	B	B
14.	218	C	C	C	B	B
15.	226	C	C	C	C	B
16.	267	C	C	C	C	C
17.	267	C	C	C	C	C
18.	320	C	C	C	C	C

Concentration=Actual blood glucose concentration in mg. per 100 ml. as determined by the Somogyi-Nelson technic.

Tube 1=A blue reaction (B) in Tube 1 represents a blood glucose level within the increment of 130-144 mg. per 100 ml.

Tube 2=A blue reaction (B) in Tube 2 represents a blood glucose level within the increment of 144-162 mg. per 100 ml.

Tube 3=A blue reaction (B) in Tube 3 represents a blood glucose level within the increment of 162-186 mg. per 100 ml.

Tube 4=A blue reaction (B) in Tube 4 represents a blood glucose level within the increment of 186-217 mg. per 100 ml.

Tube 5=A blue reaction (B) in Tube 5 represents a blood glucose level within the increment of 217-260 mg. per 100 ml.

TABLE 4

Comparison of results obtained from blood specimens analyzed for glucose content by the Somogyi-Nelson technic and the Clinitron multi-interval blood glucose method using tablet 3B

	Concentration	Tube 1	Tube 2	Tube 3	Tube 4	Tube 5
1.	198	B	B	B	B	B
2.	200	B	B	B	B	B
3.	202	B	B	B	B	B
4.	204	C	B	B	B	B
5.	204	B	B	B	B	B
6.	216	C	B	B	B	B
7.	218	C	B	B	B	B
8.	253	C	C	B	B	B
9.	257	C	C	B	B	B
10.	267	C	C	B	B	B
11.	270	C	C	C	B	B
12.	272	C	C	C	B	B
13.	280	C	C	B	B	B
14.	281	C	C	B	B	B
15.	289	C	C	B	B	B
16.	290	C	C	C	B	B
17.	320	C	C	C	B	B
18.	335	C	C	C	C	B
19.	420	C	C	C	C	C

Concentration=Actual blood glucose concentration in mg. per 100 ml. as determined by the Somogyi-Nelson technic.

Tube 1=A blue reaction (B) in Tube 1 represents a blood glucose level within the increment of 180-200 mg. per 100 ml.

Tube 2=A blue reaction (B) in Tube 2 represents a blood glucose level within the increment of 200-225 mg. per 100 ml.

Tube 3=A blue reaction (B) in Tube 3 represents a blood glucose level within the increment of 225-257 mg. per 100 ml.

Tube 4=A blue reaction (B) in Tube 4 represents a blood glucose level within the increment of 257-300 mg. per 100 ml.

Tube 5=A blue reaction (B) in Tube 5 represents a blood glucose level within the increment of 300-360 mg. per 100 ml.

Multi-interval Method for Blood Glucose Levels below 130 mg. per 100 ml.: A series of five reaction tubes containing 4.0 ml. of water is prepared. One ml. of blood is diluted with 9.0 ml. of water in a separate test tube.

1.2 ml. of blood-water mixture is added to tube 1
1.4 ml. of blood-water mixture is added to tube 2
1.6 ml. of blood-water mixture is added to tube 3
1.8 ml. of blood-water mixture is added to tube 4
2.0 ml. of blood-water mixture is added to tube 5

Blood precipitating reagent tablets No. 1 and No. 2 (zinc hydroxide) are added manually to each of the reaction tubes which are then run in the Clinitron. Since smaller increments are desired, tablet 3A is utilized. The first tube in the series showing a colorless reaction following a series of blue reactions is considered the end-point. A colorless reaction in tube No. 1 represents a blood glucose level greater than 108 mg., but less than 130 mg. per 100 ml. A colorless reaction in tube No. 2 represents a level exceeding 93 mg., but below 108 mg. per 100 ml. A colorless reaction in tube No. 3 represents a level greater than 87 mg., but below 93 mg. per 100 ml. A colorless reaction in tube No. 4 represents a level greater than 72 mg., but below 87 mg. per 100 ml. Finally, a colorless reaction in tube No. 5 represents a level greater than 65 mg., but below 72 mg. per 100 ml. Table 5 illustrates a comparison of results obtained from blood specimens analyzed for glucose content by both the Somogyi-Nelson technic and the Clinitron multi-interval blood glucose method. Blood levels of glucose less than 65 mg. per 100 ml. can be determined with this method by using blood-water mixture volumes greater than 2.0 ml.

DISCUSSION

The method described is not only reliable and ac-

curate within the stated limits, but can be utilized to advantage in a number of situations when a Clinitron is available and laboratory facilities are limited. Reasonably accurate pipetting of blood-water mixture is essential.

In addition to confirming the accuracy of the principle of the Wilkerson-Heftmann test, the data presented illustrate how blood samples can be processed for glucose values in broad or narrow increments as desired. For practical purposes it is suggested that only tablet 3A need be used, except when it is desirable to check for excessively high blood sugar values. Table 6 represents perhaps the most practicable approach, confined to the use of tablet 3A. This table illustrates the simplicity with which the operator can seek out the blood sugar interval value as soon as a preliminary specimen is run to determine whether the anticipated value is above or below 130 mg. per 100 ml. It should be remembered that an extra tablet of each reagent, 1 and 2, respectively, (zinc hydroxide reagent) must be added to each tube processed for levels below 130 mg. per 100 ml. Indeed, it is quite possible that processing such specimens at 13 mg. per 100 ml. intervals may not infrequently yield results more accurate than the Folin-Wu procedure which measures total reducing substances and may yield values of 72 to 78 mg. per 100 ml. in excess of the actual "true" glucose value.[2, 5] The deproteinization phase of the Wilkerson-Heftmann procedure, which virtually eliminates the nonglucose reducing substances, is based on the zinc hydroxide precipitation principle of Somogyi. In checking for values above 130 mg. per 100 ml. it is obviously unnecessary to process specimens at less than the proposed intervals for all practical purposes. In most instances only five tubes need be processed either above or below 130 mg. per 100 ml., as the case may be, but occasionally it may be necessary to process all seven tubes should the actual values be considerably higher or lower than anticipated.

The practical application of this test, including data on its utility and reliability, during operation of a summer camp for diabetic children, will be reported in a subsequent paper.

TABLE 5

Comparison of results obtained from blood specimens analyzed for glucose content by the Somogyi-Nelson technic and the Clinitron multi-interval blood glucose method using tablet 3A

	Concentration	Tube 1	Tube 2	Tube 3	Tube 4	Tube 5
1.	51	B	B	B	B	B
2.	61	B	B	B	B	B
3.	86	B	B	B	C	C
4.	93	B	B	C	C	C
5.	98	B	B	C	C	C
6.	100	B	B	C	C	C
7.	100	B	B	C	C	C
8.	103	B	B	C	C	C
9.	105	B	C	C	C	C
10.	110	B	C	C	C	C
11.	112	C	C	C	C	C
12.	115	B	C	C	C	C
13.	116	B	C	C	C	C
14.	117	B	C	C	C	C
15.	119	C	C	C	C	C
16.	121	B	C	C	C	C
17.	126	C	C	C	C	C
18.	126	C	C	C	C	C
19.	129	C	C	C	C	C
20.	135	C	C	C	C	C

Concentration=Actual blood glucose concentration in mg. per 100 ml. as determined by the Somogyi-Nelson technic.

Tube 1=A colorless reaction (C) in Tube 1 represents a blood glucose level within the increment of 108-130 mg. per 100 ml.

Tube 2=A colorless reaction (C) in Tube 2 represents a blood glucose level within the increment of 93-108 mg. per 100 ml.

Tube 3=A colorless reaction (C) in Tube 3 represents a blood glucose level within the increment of 87-93 mg. per 100 ml.

Tube 4=A colorless reaction (C) in Tube 4 represents a blood glucose level within the increment of 72-87 mg. per 100 ml.

Tube 5=A colorless reaction (C) in Tube 5 represents a blood glucose level within the increment of 65-72 mg. per 100 ml.

TABLE 6

Suggested clinical application of the multi-interval blood glucose method utilizing tablet 3A

Reaction tube number	Ml. of 1:10 blood-water mixture	Results in blood glucose increments (mg. per 100 ml.)
7	2.4	54-59
6	2.2	59-65
5	2.0	65-72
4	1.8	72-87
3	1.6	87-93
2	1.4	93-108
1	1.2	108-130
	0.1 ml. *undiluted* blood is first processed for 130 mg. per 100 ml. screening level.	
1	0.9	130-144
2	0.8	144-162
3	0.7	162-186
4	0.6	186-217
5	0.5	217-260
6	0.4	260-325
7	0.3	325-433

Working table which can be utilized for processing blood samples previously diluted 1:10 with water. It should be noted that each undiluted blood specimen must first be screened for the 130 mg. per 100 ml. level (using 0.1 ml.) to determine whether specimens should be processed for intervals above or below 130 mg. per 100 ml. (See text). One extra zinc hydroxide reagent tablet must be added to each specimen processed for levels below 130 mg. per 100 ml.

SUMMARY AND CONCLUSIONS

Reagent tablets originally manufactured for the Wilkerson-Heftmann blood sugar screening test are evaluated in terms of both their accuracy and usefulness in a so-called multi-interval blood glucose method, utilizing the Clinitron.

In principle, the method proposed involves four steps:

1. "Screen" 0.1 cc. of the undiluted blood sample to determine whether the anticipated value is above or below 130 mg. per 100 ml.

2. Dilute the blood specimen 1:10 with distilled water.

3. Pipette a series of volumes of the above mixture into reaction tubes, each containing 4 ml. of distilled water.

4. Place tubes in the Clinitron and read the end-point for each series of tubes.

This method has been shown to be accurate, speedy, and practical. It is especially recommended for use in small community hospitals with limited laboratory facilities, summer camps for diabetic children, and small clinics where a Clinitron is available.

SUMMARIO IN INTERLINGUA

Un Methodo, Utilisante le Clinitron, pro le Determination Multi-Intervallari de Glucosa Sanguinee

Tablettas de reagente, originalmente fabricate pro le test preselective de Wilkerson-Heftmann pro le determination de sucro sanguinee es evalutate ab le puncto de vista de lor utilitate in le si-appellate methodo multi-intervallari pro glucosa sanguinee con utilisation del Clinitron.

In principio, le methodo hic proponite consiste de quatro phases.

1. Un specimen nondiluite de 0,1 cm^3 de sanguine es preprobate pro determinar si le valor a expectar es supra o infra le nivello de 130 mg per 100 ml.

2. Le specimen de sanguine es diluite con aqua a un concentration de 1 a 10.

3. Un serie de volumines del supra-mentionate mixtura es pipettate a in tubos a reaction que omnes contine 4 ml de aqua distillate.

4. Le tubos es placiate in le Clinitron e le puncto terminal pro cata serie de tubos es determinate.

Iste methodo se ha monstrate accurate, rapide, e practic. Illo es specialmente recommendate pro uso in parve hospitales local con inadequate facilitates laboratorial, in campos de estate pro diabeticos juvenil, e in parve clinicas ubi un Clinitron es disponibile.

ACKNOWLEDGMENTS

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2. The authors express their appreciation for valuable counsel from W. E. Cornatzer, M.D., Ph.D., Professor and Chairman of the Department of Biochemistry, University of North Dakota School of Medicine.

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Errata

The following corrections should be made in the article, "Hypoadrenal Function and Adrenalectomy in Human Diabetes," by Irving Graef, M.D., which appeared in the May-June, 1956, DIABETES.

Third sentence, page 235, should read: "We know that the gluco-corticoids, epinephrine and norepinephrine all may affect carbohydrate metabolism through gluconeogenesis or glycolytic action."

Fourth sentence, second paragraph, column two, page 241, should read: "It is probable that his continued high insulin requirement (*ca* 50 units per day) is related to the large amount of adrenal steroid found necessary to prevent weakness, postural hypotension and maintain adequate serum electrolytes."

Diabetes and Pregnancy

Panel Discussion

George M. Jones, M.D., Dallas*
Chairman

George M. Guest, M.D.,† Cincinnati *Blair Holcomb, M.D.,‡ Portland, Oregon*

Robert L. Jackson, M.D.,§ Columbia, Missouri *Lester J. Palmer, M.D.,‖ Seattle*

*Jules Vieaux, M.D.,** Dallas*

CHAIRMAN JONES: We will run this panel informally. I would like to point out that this is entirely unrehearsed, and that there may be differences of opinion arising among the members of the panel as well as among members in the audience. If anyone in the audience disagrees with anything said, we offer you the opportunity to express yourself as well.

As all are aware, the problem of diabetes in pregnancy was not a matter of importance prior to thirty years ago, because before that time diabetic women just didn't become pregnant. Since then insulin has made successful pregnancy possible but new and increasing problems have emerged.

To start the panel, I would like to ask Dr. Jackson a question. He is a pediatrician and starts working with the girls. Dr. Jackson, what do you tell your young diabetic girls about the possibility of marriage and having children at some subsequent date?

DR. JACKSON: Dr. Jones, I think advice needs to be given to boys as well as girls regarding the advisability of marriage under their special circumstances. It is the obligation of the physician to inform the child and parents during childhood and especially during the adolescent period about this matter. They need to know that there is good evidence to show that diabetes may be hereditary and at least is familial. So it is very important for both boys and girls with diabetes to know that it is inadvisable for them to marry a person with a family history of the disease. Diabetics also should be advised to be very honest in informing a potential spouse that they have diabetes.

I suggest that my patients introduce their boy or girl friend to me or some other physician so the problem of possibly transmitting the disease to their children can be frankly discussed before they decide to go ahead with marriage. In my opinion, diabetics, as well as patients with other forms of hereditary disease, have the right to marry but the responsibilities of this state of life should be assumed by them. As you know, some physicians particularly interested in convulsive disorders have advocated against reproduction for any person with an abnormal electroencephalogram. If physicians should begin to advise against marriage for all patients with family histories of hereditary disease, it would leave very few people eligible for parenthood.

The girl with diabetes should also be informed about the risk she is taking if she decides to have a family. It is extremely important that girls maintain good control of their disease during childhood to prevent or delay

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the development of vascular disease during early adult life. The development of vascular disease will certainly increase the risk in pregnancy. Inasmuch as no patient can maintain continuously complete control of the disease, it is preferable for girls with diabetes to have children during the early years of their childbearing period. They should also understand the importance of maintaining good control of their disease if they are exposing themselves to pregnancy in order to decrease the possibility of their having an infant with a congenital anomaly. There is evidence that poor control, especially ketosis and acidosis, during the early weeks of pregnancy causes developmental defect in the infants of mothers with diabetes.

CHAIRMAN JONES: Is there anything you would like to add, Dr. Guest?

DR. GUEST: Yesterday in his discussion of metabolic effects of diabetic ketosis and acidosis Dr. Herbert Pollack mentioned some new observations on riboflavin metabolism which seem important in connection with what Dr. Jackson has just said. During ketonemic acidosis, in addition to the well-known loss of nitrogen and minerals from the body, Dr. Pollack noted an important loss of riboflavin. Negative nitrogen balance induced in the diabetic by withholding part of the insulin requirements or by caloric restriction resulted in an excretion of more than 50 per cent of ingested riboflavin (J. Lab. & Clin. Med. *38*:561, Oct. 1951). Long ago Dr. Josef Warkany found that in pregnant white rats riboflavin deficiency led to skeletal malformations in the developing fetus. The experimentally induced malformations in the rat occur at a critical period of fetal gestation, around the fifteenth day, before which time they are preventable, by the addition of riboflavin to the maternal diet, but not afterward. If riboflavin deficiency develops abruptly during bouts of diabetic ketosis as indicated by Dr. Pollack, such deficiency states in pregnant women might have profound effects on human fetal development and conceivably might be a factor leading to malformations in the infants of the diabetic mothers.

CHAIRMAN JONES: Dr. Palmer, by the time the diabetic girl gets into the older age group and sees you for premarital advice, do you give her any specific type of premarital examination or further instructions beyond those already mentioned?

DR. PALMER: Dr. Jones, I would like to have everyone in the audience know that Dr. Priscilla White was scheduled to be on this panel today but was prevented by circumstances from doing so, and in a very humble manner I hope to serve for her.

When I first contact the diabetic, regardless of how long they have had diabetes, I make it my business first to determine whether they know anything about diabetes, and if they do not, then they are required at least to expose themselves to a diabetic education, and I immediately see to it that they do so. I tell all my diabetic girls—I can't tell them everything Dr. Jackson has mentioned—that they should have their babies early in the childbearing years, and not wait until age has added to the difficulties that longer duration of diabetes would impose.

Now, there is some difference of opinion as to just where you should draw the line in encouraging and advising against pregnancy. I have heard Dr. Priscilla White say that they, for instance, did not advise against pregnancy even in the presence of retinitis proliferans. She said that in San Francisco at one time when we were on a panel together. Personally, I just can't quite accept that. I feel that any severe degree of retinitis, more than a mild degree, is really a contraindication to pregnancy. Of course, I think they should have at least near normal blood pressure, near normal kidney function; there should not be even moderately advanced vascular disease.

Now, there doesn't need to be any conflict between moral or religious and scientific viewpoints in this. Avoiding pregnancy, as far as I know, is no sin if accomplished by the various means and methods approved in individual religions. That will oftentimes bequite a problem to explain to some patients, but I think it has to be done before they become pregnant.

CHAIRMAN JONES: Dr. Holcomb, occasionally after a woman is pregnant the question arises, "Is this person merely pregnant or is there some other diagnostic possibility?" Would you care to mention your criteria for making a diagnosis of diabetes in a pregnant woman previously not diagnosed as diabetic?

DR. HOLCOMB: In our series of pregnancies in diabetics we have excluded the so-called "glucose-tolerance diabetics." Our most recent series consists of 52 patients over a period of 3 years, up to January 1955. I notice some series have included these so-called glucose-tolerance diabetes cases.

Whenever one finds sugar in the urine in a pregnant patient the burden on the physician is to prove that it is not due to diabetes mellitus. As you well know, during the first trimester and often following it glucose may be found in the urine of a pregnant woman and most usually this is due to a low threshold. In the latter months of pregnancy a positive test for sugar in the urine may be due to lactosuria. In order to prove the presence of diabetes we usually give the

patient a high carbohydrate breakfast containing hotcakes and syrup and do a blood sugar and a urinalysis an hour to an hour and a half later. If the blood sugar is in the diabetic range a diagnosis of diabetes can be made. If there is sugar in the urine and the blood sugar is normal we usually do a glucose tolerance test after three or four days of a preparatory diet. Here we may find evidence of a low threshold or we may find that the glycosuria is due to diabetes. It is, of course, possible that both a low threshold and diabetes may be present in the same patient, although this is rare.

CHAIRMAN JONES: Dr. Palmer, would you care to discuss for us the effect of pregnancy on diabetes?

DR. PALMER: Well, again, there is difference of opinion. I think, individually, we have all seen many diabetic girls go through pregnancy, and can certify from their records that we can determine very little change in the diabetes due to the pregnancy. This, of course, must depend upon the care the patient gets during the pregnancy. I am quite sure that pregnancy is a stress and strain on diabetics. It does cause a marked alteration of the endocrine system even among the nondiabetics, and diabetes being an endocrine disease, there cannot help but be an effect unless all possible measures are taken to offset these influences.

CHAIRMAN JONES: While you are mentioning that point, I might bring up another question: Do you think pregnant diabetic patients should be given ACTH, or some cortisone product that might still further increase the intensity or severity of the diabetes?

DR. PALMER: Don't you mean to ask whether those preparations should be avoided?

CHAIRMAN JONES: Yes.

DR. PALMER: Well, I am very hesitant to use any of the adrenal hormones in any diabetic, pregnant or not, because I have seen some patients kept on modest doses for a long period of time, who became serious problems. We avoid using these hormones in our diabetics, unless we must resort to them as a very last measure.

CHAIRMAN JONES: I agree that in pregnant women who do not have diabetes, as well as in those who do, the 17-ketosteroids are always markedly elevated. As a matter of fact, sometimes they are sufficiently elevated to make an erroneous diagnosis of Cushing's syndrome, were it not known that the individual were pregnant at the time. To add adrenal hormones would probably be disadvantageous to the patient.

I would like to ask Dr. Vieaux at this point what he thinks of the effect of diabetes on pregnancy?

DR. VIEAUX: That is a long story. There are numerous effects of diabetes on pregnancy. It may cause more early abortion, although not much more. Allowing for an average of about 10 per cent, in diabetes you may see anywhere up to 20 per cent.

We certainly see an increase in toxemia in diabetes. The diagnosis, however, may be difficult late in pregnancy because of the hypertension, proteinuria, and edema which may accompany diabetes.

There certainly is a higher incidence of large fetuses. Babies over ten pounds probably don't average more than 3 per cent in general. Now, in diabetics that figure may jump to 15 to 25 per cent.

As to fetal abnormalities, there again, there is quite a variation. Assuming that we normally have somewhere between 2 and 4 per cent fetal abnormalities, it may run up to 10 or 12 per cent.

Those are the chief effects that I can think of offhand. Someone said that there have been more malpresentations. I don't believe I have seen that. It has been said that breech incidence, for instance, is increased ten times, from usually about 3.5 per cent up to 30 per cent, but I don't believe we ordinarily see so many. And compound presentations—I have seen none.

CHAIRMAN JONES: Dr. Guest.

DR. GUEST: In view of what Dr. Vieaux said, it is pertinent to mention here the studies of Professor Hoet of Louvain, Belgium. He has stressed the importance of what has been commonly called benign transient glycosuria of pregnancy. He believes that glycosuria during pregnancy is not necessarily "benign" but indicates true diabetes mellitus, transient though it may be. He claims that some women who had had infants with malformations and who in their next pregnancies received insulin, when they developed glycosuria, subsequently delivered normal babies. Many of you know that Dr. Hoet's observations are being followed up in an extensive study at Boston at the present time.

CHAIRMAN JONES: Dr. Palmer.

DR. PALMER: As long as you referred that cortisone question to me, there are two things I think I should mention—two phenomena that are seen by everyone interested in pregnancy in diabetics: One, is the very abrupt and sharp drop in the insulin requirement following delivery, and the other is the greatly increased incidence of hydramnios. There are studies related to the ketosteroid content of the hydramnios fluid, and along various other lines to clarify further these phases of the subject. It is highly probable that hydramnios and the ketosteroids are relatable.

CHAIRMAN JONES: Dr. Holcomb.

DR. HOLCOMB: Dr. Vieaux, may I ask you a question? What is the incidence of hydramnios in nondiabetic women?

DR. VIEAUX: The incidence of hydramnios, of the more or less gradually developing type, in nondiabetic women ranges anywhere from 1 in 200 pregnancies up to 1 in 700. The acute type runs one in twelve or thirteen thousand. Now, in diabetes, the average is probably 1 in 10.

DR. HOLCOMB: Ours ran 14 per cent. What about your fetal anomalies; what is the figure on that?

DR. VIEAUX: We have no figures. At Southwestern Medical School of the University of Texas we haven't had very close control of diabetes, as such. Many of the patients come in late or ready to deliver. I do not believe any figures have been compiled since back in 1948-49. In general, they were not good.

DR. PALMER: The incidence in the literature of congenital anomalies in children of diabetic mothers is commonly spoken of as about five to one for nondiabetic mothers.

DR. VIEAUX: I believe Dr. Ralph Reese reported something like 2 to 3 per cent. The average is normally about 2 to 4 per cent.

CHAIRMAN JONES: I'd like to ask Dr. Vieaux, from the obstetrician's viewpoint, if it matters how well the diabetes is controlled during the pregnancy?

DR. VIEAUX: As far as I know, with regards to fetal abnormalities, it doesn't.

CHAIRMAN JONES: I think we might have a lot of argument about that point. Have you anything to say about that, Dr. Holcomb?

DR. HOLCOMB: I think control has an enormous influence upon the survival of the fetus, and certainly on the viability.

I'd like to say that we are very proud of these figures, if I may present them. Of our last fifty-two patients, up to January 1955, and studied over a three-year period, we have a survival of 92 per cent without use of any hormones. We have a viability of 96 per cent. Now, those figures compare very favorably with Dr. White's series of one hundred and sixty-three cases; hers was 90 per cent, as against our 92 per cent survival. Her viability rate, however, was 78 per cent, as against our 96 per cent in our series. Now, as to the control of diabetes, it was meticulous. Only two patients in this series ever had any acidosis during pregnancy, and it was very mild. Frequent, that is, weekly, conferences with the patient, occurring on the same day that the obstetrician saw the patient, were extremely important. It was good teamwork. About 80 per cent of our patients were handled by one obstetrical team, and close cooperation between the internist and the obstetrician, I think, was responsible for the good result, plus the demanding of meticulous control of the patient.

DR. JACKSON: What were the weights of the babies?

DR. HOLCOMB: Of the 52 babies, 16 weighed less than 7 pounds; 15, between 7 and 8 pounds, and 19 between 8 and 10 pounds.

DR. VIEAUX: As far as that last question goes, I thought Dr. Jones was referring to fetal abnormalities. Certainly the course of a pregnant diabetic is entirely dependent on the control of the diabetes. I haven't had any experience with hormone control, and there seem to be a lot of mixed opinions about it. But we are very much dependent upon the internist to control the diabetes in order to get healthy babies.

DR. JACKSON: The evidence from the literature does show an interrelationship between the degree of control during the early weeks of pregnancy and the incidence of congenital anomaly, also some relationship between the type of anomaly and the time during early pregnancy when they have poor control, especially episodes of ketosis or acidosis. The reason I asked Dr. Holcomb about the weights of the babies, I am sure is obvious. We observed some correlation between the weight of the term infants and the degree of control of the mother during pregnancy. It is generally stated that babies of diabetic mothers are large and overweight. It is true that a high percentage of them are, but patients who are well controlled during pregnancy may have babies within the normal weight range and of normal maturity.

CHAIRMAN JONES: Dr. Guest.

DR. GUEST: While we are discussing diabetic control in relation to fetal development and fetal anomalies let me make a plea for close and accurate observation of the time during pregnancy at which any serious crisis of ketosis has developed. Remember that the fetal injury that results from German measles in pregnant women occurs within a very narrow period of a few days during gestation. It is worth-while to recall again Dr. Pollack's observation on loss of riboflavin during ketosis. If that is a critical factor, it may have great significance early in pregnancy, but in late pregnancy it may have much less significance, when the fetus is less susceptible to injury. The period of injury by reason of such deficiency might be within only a very few days during the period of early fetal development.

DR. SHAPIRO (*New York*): (Question from audience.) Dr. Holcomb, what was the method of termination of the delivery in your cases?

DR. HOLCOMB: Prefacing the answer to your question,

I want to say something I omitted when I discussed the important factors in survival and viability.

During the last four years we have X-rayed the fetus, beginning at the estimated thirty-second week, for evidence of calcification in the epiphysis. Eighty per cent of these fetuses showed calcification of the femoral epiphysis prior to delivery. In some instances we waited through the estimated thirty-ninth week before calcification was detected, and in the remainder, because of this long period of gestation, the period added to the size of the baby and delivery was carried out without the spots being evident. Most of the babies showed calcification of the femoral epiphysis immediately following delivery. Most of these patients had cesarean section, of the primipara, 16 of 18; of the multipara, 24 of 32. Does that answer your question?

DR. SHAPIRO: It answers it in part. I meant to refer to the discussion about weight as a function of control, and which would be affected by the date and time of delivery. Delivery in your patients, then, was two to four weeks before the anticipated expected date; is that correct?

DR. HOLCOMB: Yes, averaging around the estimated thirty-seventh week. We think the X-ray procedure is valuable.

DR. VIEAUX: Dr. Jones, I wanted to ask Dr. Holcomb what he thinks is the responsible factor for the large fetuses?

DR. HOLCOMB: Well, does somebody else want to discuss this question?

DR. JACKSON: Approximately 80 per cent of infants born of diabetic mothers have a birth weight above the average for the period of gestation. The size of the infants appears to be due to three factors: edema, obesity, and splanchnomegaly. The edema of the infants at birth is generalized, nonpitting, but strikingly demonstrated by the considerable weight loss in the first forty-eight hours after birth. This increased extracellular fluid well may be related to hormonal imbalance of the mother. There is good evidence for transplacental transfer of hormones. The obesity is often explained as a result of increased insulin output by the infant's pancreas to compensate for the high sugar content of the mother's blood. Hyperplasia of the infant's pancreatic islets of Langerhans is a characteristic autopsy finding. Hormonal imbalance (excessive growth hormones) also has been suggested as the cause of the enlarged liver, spleen and heart of these infants. Dr. Edith Potter has questioned if there is true splanchnomegaly.

DR. VIEAUX: I believe that these babies are also large throughout the course of the prenatal period. Therefore, what do you think about the growth factor from the pituitary playing a part?

DR. JACKSON: The infants are premature by length and behavior rather than postmature. Of course, they may be large throughout gestation because of the tendency toward edema and obesity. The infants, to my knowledge, do not have an increased body length or bone age. We badly need more detailed data to answer this pertinent question.

CHAIRMAN JONES: Dr. Vieaux, I'd like to ask another question, if you don't mind. If a woman with well-controlled diabetes is pregnant, do you think she is obstetrically normal?

DR. VIEAUX: We never look upon a diabetic pregnancy as a normal pregnancy. They are probably normal for diabetes, but there is always the hazard of fetal death in utero during the last two or three weeks, which may or may not be due to toxemia or acidosis. There are still some infants who will die for no apparent reason. So, any diabetic pregnancy is viewed with apprehension.

CHAIRMAN JONES: Obstetrically, how is the labor and the pregnancy treated differently from that of a healthy nondiabetic woman?

DR. VIEAUX: If one is of the school that believes that the controlled diabetics should be allowed to go to term and into spontaneous labor, then obstetrically they are handled no differently from any patient. At that time we turn the diabetic control over to the internist, and let him worry about the details. However, most of us feel it is well to induce labor somewhere between 35 and 37 weeks. Now, whether labor can be induced, or whether a cesarean section should be done will depend on such ordinary obstetrical indications as pelvic disproportion. If a long labor is anticipated, as in a primipara, or abnormal presentation, section is preferable. If the cervix is shortened and dilated, the fetus well down in the pelvis, and the cervix is ripe, why then it is probably safe to try induction. In the elderly primigravida, say over the age of thirty-five, or a mother who has had repeated dead babies, again section is indicated. If there is a long "green" cervix with a floating head, especially in the presence of hydramnios, where rupture of the membranes may be associated with prolapsed cord, those patients should also be sectioned.

DR. HOLCOMB: Dr. Vieaux, may I add that one of the reasons we like to have cesarean section done early in the day is the same reason for our request to surgeons to schedule elective surgery on diabetic patients at 8:00 a.m. Planning insulin dosage and fluid intake is much easier when the time factor can be controlled. Long labor introduces difficulties both for the mother

and baby from a diabetic standpoint.

CHAIRMAN JONES: It may be a nice way to anticipate your program, but I am wondering now, from the pediatric viewpoint, what is the difference in hyaline membrane disease in babies delivered by cesarean section, as compared to those through normal delivery?

DR. JACKSON: Well, it is certainly true that of the babies born of diabetic mothers, a high percentage of them are dying after the second or third day, with typical pathological finding of hyaline membrane disease, and this is easily correlated with the fact that these babies are somewhat immature at birth and a high percentage of them have been born by cesarean section. Premature infants of nondiabetic mothers born by cesarean section also have a high incidence of hyaline membrane disease. The possibility exists that the incidence of this disease in infants of diabetic mothers is related to the maturity and method of delivery rather than to the disturbed metabolism. The question arises as to whether or not diabetic mothers in good control can safely be carried to term and be delivered without section. The fact remains that many diabetic patients have had silent intra-uterine deaths and many obstetricians believe it is advisable to interrupt pregnancy about twenty-one days before the expected date. I think we need carefully controlled research studies to determine better the indication for interrupting pregnancy.

CHAIRMAN JONES: Well, I know certainly that Dr. Mengert's viewpoint was that he would avoid doing cesarean section as much as possible in delivery of these babies. Isn't that right, Dr. Vieaux?

DR. VIEAUX: Oh, yes.

CHAIRMAN JONES: Have you any further comment on that, Dr. Guest?

DR. GUEST: Dr. Harvey Knowles gave me permission to quote the figures on experiences in the Cincinnati General Hospital. Prior to the end of 1953 there had been 50 per cent mortality among babies born of diabetic women. At the end of 1953 a "diabetic team" was organized with members of the department of internal medicine cooperating with the staff of the obstetrical service.

In 1954 and 1955 there were 32 successive pregnancies in diabetic women. Of these 20 were followed throughout pregnancy by the diabetic team; 12 were delivered by cesarean section. Nineteen of their infants survived and one died in the neonatal period, giving a fetal survival of 95 per cent. Among the 32 women 12 had not been followed through pregnancy by the team but were first seen just before delivery. None of these was delivered by cesarean section. Of these 12 infants 8 lived, giving a fetal survival of 67 per cent.

Until the present time these women have been receiving stilbestrol, but Dr. Knowles states that this is now regarded as a debatable matter. A point stressed by the team is that at the time of delivery clearing of the air passages of the baby by suction is very important.

DR. PALMER: Dr. Jones, I don't believe we should leave this subject of when to deliver a diabetic mother, without this comment: Any obstetrician who has selected the date of delivery of a diabetic mother, regardless of how you compute the duration of the pregnancy—and there are all sorts of methods—is still walking a tightrope. Now, the reason I say that is because, when our obstetrician, on one or two occasions, has said, "This baby is pretty small; everything seems to be all right, blood pressure, kidneys, everything is going along all right; we had better wait." And then, we still set it a week ahead, because we are not sure of the age of the pregnancy, and I don't think you ever can be. I don't think the obstetrician, with diabetic or nondiabetic women, is ever quite sure just how old the pregnancy is. Now, we have had this experience: When we listened for the heart tones the night before the cesarean was scheduled, we found them, and the next morning, on the way to surgery, we couldn't find them. So that is why I say—it is walking a tightrope, and an individual problem. There is probably never going to be any formula which will apply to all patients, informing the attending physicians of the absolutely optimal date to deliver the fetus.

I wish to make this additional remark about statistics in general. Although I do not believe that authors who publish statistical papers intend to mislead the readers, I am certain that statistical papers must be carefully prepared and all of the influencing factors be stated. Otherwise, statistical papers may be very misleading, and they should be carefully studied and interpreted in relationship to other reports. I well remember in Dr. White's early series, I found that she was eliminating all pregnancies that did not reach the age of viability. And I said I didn't think that was fair, for comparison with nondiabetic groups. I believe after the first third or so of her series she began including all pregnancies, and rating the statistical fetal survival on that basis. You can see what I mean about how variably you can interpret figures, whether you are talking about juvenile diabetics or older diabetics, whether you are talking about the first, second or third pregnancy. You may recall a group reported from Iowa by Dr. Jackson, a few years ago—remember, when they were talking about

a group of "cornfed" mothers down there who had three babies apiece, and then developed a mild diabetes? They did not have any fetal mortality or maternal mortality, or any unusual complications. They did not believe that pregnancy in the diabetic constituted a major problem.

DR. VIEAUX: Regarding the estimation of fetal size, that is one of our greatest sources of error. Yesterday, I spoke with Dr. Jack Prichard, who is head of our obstetrical department. He said in diabetics he usually estimated the fetal size and then added a pound or two!

Of course, we have tried by X ray to demonstrate the distal femoral epiphysis, although some say the proximal tibial epiphysis is a more accurate guide. But I think it all boils down to what one thinks the baby's size is from palpation, the state of the diabetes, and the other aforementioned factors that go into making a decision as to when to do a section or induce labor.

CHAIRMAN JONES: I am sure that all of us would wholeheartedly agree that the state of control of the diabetes during the pregnancy is a most important factor. I am just curious to know if any members of the panel have their diabetic pregnant women routinely admitted to the hospital every month or so for check-up control, as they do in certain centers? I, personally, don't, because I feel that I can keep my patients well controlled prior to hospitalization for delivery, but I am interested in whether the other members of the panel agree or disagree with that viewpoint.

DR. HOLCOMB: Our patients haven't been hospitalized until one or two days before planned cesarean section or induced labor.

DR. VIEAUX: Dr. Guest just pointed out that in the observations on prediabetic mothers during the five-year period before development of diabetes, newborn babies are large, and probably larger than those delivered during the course of diabetes. The neonatal mortality is the same.

CHAIRMAN JONES: So far, nothing has been said about the place of the diabetic diets during pregnancy. Would you care to discuss that, Dr. Holcomb?

DR. HOLCOMB: We do not change the diet appreciably, assuming we are dealing with a patient who has had diabetes for a fair period before pregnancy occurs. We do not change the diet in the first three months, but later we increase the protein, and decrease the fat, especially if the weight increases.

CHAIRMAN JONES: Dr. Palmer, would you care to make any comment on the control of the diabetes during the immediate phase of delivery, whether by labor or by cesarean section?

DR. PALMER: Well, having set the date, as to when we are going to deliver the diabetic mother, if she hasn't gone into spontaneous labor by that date, we do a cesarean. Now, if we are going to do a cesarean, the approach is the same as it would be for any surgical diabetic. If she is going into labor, I think one thing we have to remember is that labor is terrific exercise, and therefore, there must be adequate carbohydrate in the diet; and you have to be somewhat watchful that hypoglycemia does not develop during spontaneous labor, which is a good deal like running around the block twenty-four hours a day.

CHAIRMAN JONES: I certainly agree. More frequently during the course of delivery, a woman may become somewhat nauseated or may vomit, in which case the carbohydrates must be adequately replaced, if necessary by intravenous glucose. I believe that the termination of pregnancy is the time when we have to be most careful to avoid hypoglycemia for the mother, at least shortly following delivery.

This brings up a point I would like to ask of Dr. Guest: Do you think, from the evidence we have available that there is any oversecretion of insulin by the fetus, and are these particular offspring more likely to become hypoglycemic following delivery than other newborn?

DR. GUEST: That has been postulated. Dr. Jackson mentioned that the babies of diabetic mothers show hyperplasia of the islet beta cells. When it was first observed that these infants often had hypoglycemia a common practice was to give glucose solutions by mouth and intravenously. Later, other observers making a careful study of infants of *nondiabetic* mothers noted that their blood sugar very often falls to approximately the same low level. After such observations there has been less insistence upon routine administration of glucose. It should be mentioned that some of the babies in the neonatal period with twitching which might be thought to be caused by hypoglycemia, are suffering from hypocalcemia. In our experience such hypocalcemic tetany has most often been observed in the infants who were slightly edematous. In such babies the administration of calcium chloride is indicated rather than glucose.

DR. HOLCOMB: Dr. Jones, relative to the matter of increased dosage of insulin during the latter months of pregnancy, 66 per cent of our patients required more insulin, and 34 per cent less insulin during pregnancy.

There is one point of practical importance, and that is, we have diligently instructed diabetic mothers during pregnancy not to take any insulin in the thighs for obvious reasons. We have seen some prolonged hypo-

glycemia following cesarean or spontaneous delivery because of the release of insulin from large indurated areas, especially if there was edema in the thighs. They have been instructed to inject insulin under the abdominal skin. This is distasteful to some women, and sometimes a little difficult to do. And so, in the past few years we have routinely been instructing the husbands in the technic of injecting insulin along the spine or below the angles of the scapula, where the skin can be picked up readily. Since we have done that, we have seen fewer women need to take increasing dosage during pregnancy.

CHAIRMAN JONES: I would like to ask Dr. Jackson one question: Does the type of anesthesia and analgesia given the diabetic mother prior to delivery of the baby have much effect on the fetal outcome?

DR. JACKSON: I don't know the answer. I'll pass that to somebody else.

DR. PALMER: I don't think there is any question about that. The amount of sedation used, the type of anesthesia used for the natural delivery or for the cesarean section is quite a factor. I would like to emphasize that the younger the mother develops diabetes, and the longer she has had it, the lower is going to be the rate of fetal survival.

DR. HOLCOMB: All of our cesareans were done under spinal anesthesia. No demerol or sedative was given the mothers until after delivery.

CHAIRMAN JONES: I'd like to ask our pediatricians on the panel again—what about the immediate management of the infant born of the diabetic mother?

DR. JACKSON: A baby born of a diabetic mother should first of all have his airways established, as has been mentioned by Dr. Guest. It is also wise to empty the stomach because of the increased amounts of amniotic fluid frequently found in the stomach. The baby is then placed face downward in an environment of high humidity. If there is any respiratory distress, oxygen should be given, but no higher than 40 per cent. The baby should be observed carefully. In general, we do not give any glucose unless there is a history of inadequate fluid intake by the mother, which was mentioned by Dr. Palmer. Dr. Gellis, of Boston, has shown that very occasionally these infants do have hypoglycemia. The maternal history is very important. All babies are watched very carefully, and if there is any twitching, as Dr. Guest mentioned, the infant is given both calcium and glucose. However, there are two considerations worthy of mentioning. (1) Where signs suggestive of Cushing's syndrome are present ACTH or cortisone may be indicated to compensate for rapid withdrawal of maternal hormones. There also is evidence that some of these babies die of cardiac failure and I think it would be interesting for some of us to do serial electrocardiograms to see if there is evidence of hypokalemia in some of these infants. It is evident from these remarks that additional research studies need to be made to define better the pathological physiology of this entity.

DR. PALMER: What about dehydration following delivery, Dr. Jackson?

DR. JACKSON: Special precautions should be taken to avoid giving sodium-containing fluids. Unless there is a definite indication, as mentioned above, we withhold oral feedings until about forty-eight hours after birth.

CHAIRMAN JONES: I would like to ask the members of the panel what are their specific contraindications to pregnancy in the diabetic mother? Dr Palmer, would you care to state yours?

DR. PALMER: I referred to that a little before. I think that the prepregnancy examination, as I like to call it, should show at least a minimum of vascular degeneration by X ray; that if the patient is past twenty-five, she should have an electrocardiogram. The renal function should be studied and the eye grounds should be carefully observed, and any severe degree, or even moderately severe degree of retinal damage should, in my opinion, be a contraindication to pregnancy. I have seen too many eyes deteriorate severely during pregnancy, and I believe that a semiblind mother cannot be an efficient mother. On the other hand, Dr. White states that she has seen retinal improvement during pregnancy.

CHAIRMAN JONES: I'd like to ask if the members of the panel think there are any indications for therapeutic abortion in diabetic pregnancy? Dr. Vieaux?

DR. VIEAUX: The only indications are arteriosclerosis of the pelvic arteries, retinitis, and possibly glomerulosclerosis with definite impairment of renal function. Ordinarily, I wouldn't feel that pregnancy should influence the uncomplicated diabetic. Pregnancy may increase pre-existing hypertension in the diabetic. I don't believe that with the milder forms of diabetes one would have any particular trouble.

CHAIRMAN JONES: Well, I agree that the diabetic without degenerative complications is less likely to have trouble, but can you be any more specific regarding the time to tell a patient that she ought to have a therapeutic abortion? For instance, you said pelvic arteriosclerosis. I have seen two diabetic women with calcification of the pelvic vessels, who came through their deliveries perfectly normally and got along well. I wouldn't consider that an indication for therapeutic abortion.

DR. VIEAUX: I think we are probably more concerned about the future of the mother. There are really very few indications for a therapeutic abortion, as far as I can see.

CHAIRMAN JONES: That is just what I was trying to point out. I don't think there are very many indications for it either. I'd be glad to hear Dr. Palmer's viewpoint, if he disagrees.

DR. PALMER: I am not going to answer that question. I'll let Dr. Holcomb answer that one. But I do want to say, as Dr. White has said, after twenty-five years of diabetes, you will find very few diabetic women who will pass a satisfactory prepregnancy examination.

DR. HOLCOMB: We had just one therapeutic abortion in our series.

In fairness to my two associates, Dr. John W. Stephens and Dr. Otto C. Page, both of whom received training under Dr. Priscilla White, I want to state that at least two-thirds of the series I have discussed today was entirely supervised by them. I am sorry they couldn't be here.

There is one other point which ought to be clarified, Dr. Jones. In quoting our statistics about survival and viability, I think it only fair to point out that many reported series have not taken into consideration the duration of the diabetes, nor the age of development. When those factors are evaluated, it gives us a better appraisal of Dr. White's work. In her series, classifying according to her pregnancy-risk classifications, A, B, C, D, E and F, 71.8 per cent of her patients were in the C, D, E and F groups; whereas, we had 60 per cent in these groups.

With an onset below age ten, she had 20 per cent and we had 28 per cent. In the onset before age twenty, she had 66 per cent and we had 60 per cent. So they are reasonably comparable.

CHAIRMAN JONES: I have a letter written to me by Dr. Max Miller. I told him I was going to appear on this panel, and he sent me his up-to-date figures, also using the classifications of Priscilla White on a total of 174 pregnancies treated at the University Hospital in Cleveland.

In his classes C, D, E and F, there was a fetal mortality rate of 21.8 per cent in the years between 1931 and 1950, and 17.2 per cent in the years from 1950 to 1955, and these happen to be almost one-half of the total of the series. Two of his patients who died in the 1950-55 era in this group had ketosis, which he thought were completely avoidable deaths. So his corrected fetal mortality in this group of patients, not giving them any type of hormones at all during pregnancy, was 10.4 per cent, which compared very well with Dr. Priscilla White's hormone-treated group.

I don't know whether we will have an opportunity for everybody to state what he thinks, but the question remains as to the use of hormones in diabetic pregnancies.

DR. PALMER: Our experience has varied a great deal. Our total series of pregnant diabetics has been divided in groups of fifty patients per group, and for each group we have employed a different system. In some we had so-called adequate or ample hormone supplements, and in some we had none at all. At the present, we are not employing any at all. We are placing the major emphasis on a meticulous control of the diabetes, which means seeing the internist and the obstetrician once a week during the last three or four months of pregnancy, and every two weeks preceding that.

CHAIRMAN JONES: Dr. Holcomb, have you any comment on this aspect?

DR. HOLCOMB: We haven't used any hormones for the past seven years, and when we did use hormones, I am sure the dosage was grossly inadequate even with stilbestrol. We have never used progesterone.

DR. VIEAUX: My experience has been mainly with oral stilbestrol, and it did not seem to alter the course of the pregnancy whatsoever.

Now, of course, Dr. Priscilla White recommends the injectable varieties. I stopped in at a drugstore yesterday and found that both Lilly and Upjohn provide a 1 cc. ampule of stilbestrol containing 25 mg. costing $2.25. The Vitamix Corporation puts out 10 mg. per cc. in 30 cc. vials for $4.00. Now, to the patient, the 30 cc. of 25 mg. per cc. costs $10.25, and 10 cc. of 50 mg. per cc., $12.75. The milder diabetic gets a dosage up to 200 mg. per day of stilbestrol and progesterone; in the more severe, 250 mg. per day.

I believe Dr. DeCosta figures out that for the milder type of diabetic, the average cost would run pretty close to $450.00, and the severe type, $650.00. Dr. Prichard said when he was at Cleveland, they figured the cost to run around $800.00. Now, how many patients can afford that? And, with no more assurance that one is going to get good results.

CHAIRMAN JONES: I certainly agree with that point of view. I am sorry that Dr. White is not here today to defend her program. But if Dr. Max Miller's figures are correct—and I have no reason to doubt his statements—he is gathering a large series in which patients, even with the more severe types of diabetes, are getting along as well as Dr. White's hormone-treated series.

In the Oct. 22, 1955, issue of *Lancet* is the report

to the Medical Research Council by their conference on diabetes and pregnancy which agrees with Dr. Miller's findings of no difference in maternal or fetal survival, or complications in the hormone and nonhormone treated groups.

DR. OPPENHEIMER (*St. Louis*): (Question from audience.) At previous meetings Dr. White mentioned the use of veterinarian hormones to reduce the cost to the patient. I had an opportunity to treat a patient who was in Class F, according to her series, and getting veterinarian hormones, both stilbestrol and progesterone, suppository base. The cost, at the veterinarian's price, to treat the patient according to the dosage which she suggests, is about $130.00. Now that is still a lot of money, but a far cry from $400, $600 and $800.

CHAIRMAN JONES: Thank you, Dr. Oppenheimer. The meeting is concluded. My thanks to the members of the panel for their part in this discussion.

Combating the Food Faddists

Where does the public obtain nutrition information—authentic and otherwise? Newspapers, radio, television and emotional dissertations in public halls are media over which the dietitian has limited control. But what about public libraries? How can librarians keep abreast of the authentic books in the field of nutrition when so many that represent the twilight zone of knowledge become best sellers? Members of the Michigan Dietetic Association have been concerned about the dearth of reliable information available on the shelves of some libraries, and have offered their services to the State Library. A suggested list of pamphlets and books that might be considered for purchase by local libraries has been compiled and an exhibit of these publications is on loan from the State Library. The suggestions are realistic and inexpensive. One group of pamphlets and books will cost only $5.05, another $10.50, and still another $16.45. Librarians who have been contacted welcome this assistance and some have asked a dietitian to offer advice relative to the nutrition books currently in the library. If you should examine the library shelves in your home town I hope you would be pleasantly surprised. However, there is reason to conjecture that many of you will be alarmed! For example, the public will not become very enlightened by reading a 1928 volume in this field, nor will they be helped by reading a modern version of a fairy tale approach promising the wonders of the world through the consumption of blackstrap molasses, or any other 'wonder food.' The Michigan Dietetic Association plans to revise continually their suggested list of pamphlets and books so that our libraries may have a continuing service—it is our challenge to encourage them to use it.

Nutritionists rely heavily on the professional and/or legal authority of the Food and Drug Administration, the Federal Trade Commission, the American Medical Association, the Food and Nutrition Board and other professional groups. We need all the help that can be given us so that we may have the facts about the people and the products threatening at most, the health, at least, the pocketbook of the consumer. Can information about unethical people, pamphlets and products that relate to the field of nutrition, be disseminated to the professional groups regularly? For example, nutritionists would find it helpful to know something about the ethics and the methodology of the folks who sell 'sterile stainless steel' before they arrive in town rather than after they have left—several thousand dollars richer and a few hundred people closer to self-diagnosis and farther from seeking adequate medical care.

. . . The American Medical Association has been of tremendous service to us in the past through the publication of information about people and products whose procedures and promises were something less than ethical. Nutritionists and all other readers of the *Journal of the American Medical Association* would be served if the Association would again assume an aggressive approach in the presentation of such information; little of this nature has been published within recent years. . . .

The words, "doctors approve," are magic; as a professional ally of the physician, the nutritionist finds it difficult to counteract those words in an advertisement. Would it not be a worthy project for the American Medical Association if they were to study the present widespread use of this claim and learn whether it is, or is not, a figment of a slick advertiser's imagination?

From the School of Public Health, University of Michigan, Ann Arbor, by Adelia M. Beeuwkes in *Federation Proceedings* 13:785-89, September 1954.

Recent Statistics on Diabetes

Provisional figures for 1955 indicate that the number of deaths in the United States ascribed to diabetes was approximately 25,000 during the year. The death rate was 15.3 per 100,000, slightly less than the 15.4 recorded in 1954 (table 1). The 1955 rate was appreciably less than in prior years as far back as 1949, when the Sixth Revision of the International List first came into use. Provisional data for 1955 for the urban wage-earning population, represented by the industrial policyholders of the Metropolitan Life Insurance Company, likewise show little change in diabetes mortality from 1954—the death rates from the disease being 14.9 and 14.8 respectively in the two years. The situation in the last six months of 1955 showed slight improvement over the first six months when, in both the national and the insurance company experiences, modest increases in the diabetes death rate were recorded over the corresponding period of 1954. The maintenance of the rate in 1955 at the level of the preceding year should be considered in the light of various factors which adversely affect diabetics and because of which some rise in the death rate from the disease might be expected. These are the rather widespread outbreaks of respiratory disease early in 1955, a prolonged and widespread heat spell during the summer, and the steady increase in the proportion of older persons in the population. On the other hand, there appears to be a continuing tendency on the part of physicians to ascribe fewer deaths of diabetics to the disease.

The several cities and states from which data are obtained regularly show, in general, some increase in the death rate from diabetes in 1955 as compared with 1954. The rise was particularly large for New York City and accounts for most, if not all, of the recorded increase in New York State. In like manner, the rise in Baltimore is rather large and accounts for most, if not all, of the recorded rise in the State of Maryland. The figures for Philadelphia and Boston, on the other hand, are not strictly comparable with those of a year ago.

Both of Canada's largest cities recorded a reduction in diabetes mortality in 1955, the decline being particularly marked for Montreal. In England, the rate for 1955 in the London Administrative County was remarkably higher than in 1954. Data for England and Wales for the first nine months of 1955 show a rise of 10 per cent over the same period of 1954. The increase was especially large among females. This rise in the diabetes rate in 1955 is a reflection of general health conditions in the country. The death rate from all causes in the first nine months of 1955 was the highest of any year since 1951. The mortality from respiratory diseases showed a particularly sharp rise in 1955.

Provisional data by region (table 2) for the United States for 1955 as compared with 1954 show, against a background of a slight decline for the country as a whole, a significant increase in the West South Central States, and significant decreases for the West North Central, and East South Central States. Elsewhere either the changes in the number of deaths in the sample or the total deaths were too small to yield reliable comparisons.

Final death rates are now available for 1953 by region and by state and are shown in table 3 along with the rates for the three preceding years 1950 to 1952 and the averages for the entire period 1950 to 1953. Few regions show any systematic changes over these four years. Probably most consistent is the increase recorded in the Middle Atlantic States. This is most strongly marked for New York State. In the East North Central States and New England the general trend has been downward.

During these four years the region with the highest rate has shifted from New England to the Middle Atlantic States. The latter has also the higher average rate for the four-year period. The level of diabetes mortality in all the regions of the South and the Far West is sharply differentiated from that in the Northern and Northeastern sections of the country. In fact, with few exceptions, the rates in the individual states in the South and Far West are all lower than in any state of the North and Northeast. The most notable exception is Delaware in which the rate has been consistently above 20 per 100,000 and which ranks fourth among the states during the period 1950 to 1953.

Throughout the period Rhode Island has maintained its position as the state with the highest death rate from diabetes in the country and second rank, based upon the average rate for the four years, is shared by

Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues from Association members and other readers of the *Journal*.

TABLE 1
Recent data on diabetes mortality
Death and death rates—1955 and 1954

Area	Death rates per 100,000		Number of deaths	
	1955	1954	1955	1954
United States (10% sample)	15.3	15.4	2,506	2,482
Metropolitan Life Ins. Co. industrial policyholders	14.9	14.8	2,698	2,705
New York State	20.4	19.8	3,247	3,121
New York City	21.1	19.4	1,693	1,571
Maryland	18.6	16.8	481	428
Baltimore, resident	21.7	18.6	210	180
Boston	18.1	19.0	147†	154
Philadelphia	21.6*	26.2	465*	563
Toronto	15.5	15.8	106	108
Montreal, resident	14.8	16.6	160	177
London (Administrative County)	8.2	6.8	273	226
	Jan.-Sept.		Jan.-Sept.	
England and Wales				
Total	7.6	6.9	2,520	2,289
Males	5.3	5.0	844	798
Females	9.7	8.7	1,676	1,491

* Resident deaths.
† Incomplete returns.
Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in "Current Mortality Analysis," a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2
Number of deaths and death rates from diabetes in geographic division;
United States reporting area for the 10 per cent sample;
1955, 1954 and 1953

Geographic division	Death rates per 100,000*			Number of deaths*		
	1955	1954	1953	1955	1954	1953
U. S. reporting area	15.3	15.4	16.0	2,506	2,482	2,539
New England	18.5	17.4	18.4	184	170	178
Middle Atlantic	20.6	20.8	22.6	674	668	702
East North Central	18.1	18.1	20.2	609	595	651
West North Central	13.4	15.1	17.3	197	220	247
South Atlantic	12.8	12.7	12.5	295	289	281
East South Central	9.3	11.0	8.9	107	126	102
West South Central	12.3	11.0	10.6	190	169	162
Mountain	10.7	7.7	9.8	63	44	55
Pacific	10.6	12.1	9.9	187	201	161

* Excludes armed forces overseas.
Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."
Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

Ohio and Pennsylvania. The lowest rates have been maintained by New Mexico and Arizona. Notable also is the low rate recorded in California. The range of the rates is surprisingly large—the highest rate over the four-year period, registered in Rhode Island, is nearly five times as high as the minimum recorded for New Mexico.

Provisional data for 1954 on diabetes mortality by age, without regard to color and sex, are now available (table 4). They show, at most ages, a slight decline from the provisional data recorded for the previous year. The only noteworthy exception is a rise in the rate at age 85 and over. The number of deaths in the sample at some ages is rather small, and caution is necessary in interpreting the differences between the two years in the rates at these ages.

Data for several years are now available on mortality

TABLE 3

Death rates per 100,000 from diabetes in the United States by geographic region and state,* 1950 to 1953

Region and State	1950-1953 (Average)	1953	1952	1951	1950
United States	16.3	16.3	16.4	16.3	16.2
New England	21.1	19.7	20.7	22.8	21.0
Maine	16.9	15.1	15.9	19.7	16.9
New Hampshire	21.2	21.1	21.8	21.9	20.1
Vermont	17.9	19.4	19.6	16.6	15.9
Massachusetts	21.3	19.0	21.5	24.2	20.5
Rhode Island	31.4	30.0	29.0	30.7	35.9
Connecticut	18.8	19.0	17.7	19.1	19.3
Middle Atlantic	21.4	22.5	21.6	20.9	20.5
New York	20.1	21.3	20.6	19.6	19.0
New Jersey	21.0	21.2	21.4	21.7	19.7
Pennsylvania	23.4	24.7	23.3	22.4	23.0
East North Central	20.0	19.5	19.8	20.2	20.6
Ohio	23.4	23.3	24.0	23.9	22.5
Indiana	17.7	17.6	18.1	17.2	17.9
Illinois	17.9	16.7	17.1	18.3	19.5
Michigan	20.8	20.5	19.8	21.1	21.9
Wisconsin	18.8	18.4	19.0	18.2	19.5
West North Central	17.4	17.3	17.5	17.0	17.9
Minnesota	16.9	17.4	16.6	16.5	17.0
Iowa	17.1	16.7	16.9	17.4	17.4
Missouri	17.6	16.8	17.7	17.4	18.5
North Dakota	17.3	15.5	16.9	19.1	17.6
South Dakota	17.1	17.8	18.0	14.7	17.8
Nebraska	19.7	21.2	19.7	18.5	19.5
Kansas	16.9	16.6	17.6	15.6	17.9
South Atlantic	12.4	12.3	12.5	12.0	12.6
Delaware	23.3	22.1	23.0	21.2	27.0
Maryland	17.6	17.6	17.9	17.9	17.0
Dist. of Columbia	13.9	13.7	13.9	12.7	15.1
Virginia	10.4	10.1	10.5	10.1	11.0
South Atlantic (con't)					
West Virginia	12.2	11.5	14.4	10.7	12.2
North Carolina	9.7	10.4	9.3	9.3	9.8
South Carolina	12.3	12.0	11.8	11.9	13.4
Georgia	12.1	11.9	12.1	12.5	12.0
Florida	12.6	12.4	13.1	12.2	12.7
East South Central	10.8	11.0	11.0	11.0	10.2
Kentucky	12.8	12.8	13.8	12.7	11.9
Tennessee	9.2	9.2	9.1	9.1	9.5
Alabama	10.2	10.8	10.2	10.7	8.9
Mississippi	11.5	11.6	11.4	12.2	10.8
West South Central	11.6	11.6	11.5	11.7	11.6
Arkansas	9.5	9.7	8.9	9.8	9.4
Louisiana	14.1	14.8	14.5	14.4	12.5
Oklahoma	13.4	14.2	13.1	12.9	13.4
Texas	10.8	10.3	10.6	11.0	11.3
Mountain	11.0	10.7	11.7	11.3	10.3
Montana	13.9	14.7	16.1	13.4	11.5
Idaho	13.9	13.1	13.4	14.9	14.1
Wyoming	13.4	14.1	11.8	16.1	11.4
Colorado	10.9	11.0	11.0	10.8	10.9
New Mexico	6.5	5.4	7.3	7.8	5.6
Arizona	8.8	8.2	10.6	7.8	8.4
Utah	12.6	12.0	14.7	12.2	11.3
Nevada	10.7	11.2	7.6	13.5	10.6
Pacific	10.8	10.9	11.0	11.1	10.0
Washington	15.2	15.3	15.1	16.0	14.2
Oregon	11.7	12.4	11.6	11.7	11.2
California	9.7	9.9	10.0	9.9	8.8

* By place of residence. Excludes Armed Forces overseas.

Source: National Office of Vital Statistics of the U. S. Public Health Service, Special Reports—National Summaries.

from diabetes, by race and sex, according to the Sixth Revision of the International List of Causes of Death. As has been noted in earlier issues, the level of mortality ascribed to diabetes was reduced sharply below that prevailing prior to the Sixth Revision. The crude death rates from diabetes since 1949 and the rates adjusted for changes in age distribution of the population are shown in table 5, along with similar data for all causes of death combined. The data reveal the recent trends in mortality from diabetes and in the proportion to all causes. Perhaps some caution is necessary in interpreting the figures for 1949 because not all the states were using the new death certificate inaugurated with the Sixth Revision nor had physicians had time to familiarize themselves with it.

For the population as a whole, for which both crude and adjusted death rates are available for the year 1954 from a 10 per cent sample of death certificates, the trend of the crude mortality is marked by a moderate decline, perhaps spurious in part, between 1949 and 1950; then a virtual stationary rate during the four-year period 1950-1953; and then a sizable decrease in 1954, which has apparently been maintained in 1955 (see table 1).

The age-adjusted death rate, which allows for the increased proportion of older persons in the population, shows somewhat the same characteristics, except for a slight downward trend in 1950-1953. The trend of the death rate from all causes has been similar. Consequently, the proportion of deaths ascribed to diabetes has remained virtually unchanged.

Among white males, during 1950-1953 the crude death rate from diabetes increased slightly, but as indicated by the age-adjusted rate, this was due primarily to the aging factor. Among white females, on the other hand, the trend for diabetes has been downward, but the proportion of diabetes deaths to those from all causes

TABLE 4
Estimated deaths and death rates from diabetes by age
United States, 1954 and 1953
(Based upon the returns from a 10 per cent sample of death certificates)

Age groups	Death rates per 100,000*		Number of deaths*	
	1954	1953	1954	1953
All ages	15.4	16.0	24,830	25,390
Under 1	0.8	0.6	30	20
1-14	0.4	0.5	190	220
15-24	1.3	1.4	270	300
25-34	2.2	2.5	520	610
35-44	4.2	4.4	940	980
45-54	11.0	12.1	2,040	2,200
55-64	38.5	41.9	5,510	5,880
65-74	91.5	93.6	8,450	8,540
75-84	152.7	158.8	5,680	5,740
85 & over	154.9	120.5	1,180	880
Not stated			20	20

* Excludes Armed Forces overseas.
Source: Monthly Vital Statistics Reports—Annual Summaries for 1954 and 1953, Part 2. National Office of Vital Statistics of U. S. Public Health Service.

has not changed significantly.

Among nonwhite males the death rates from diabetes during 1950-1953 have been relatively stable. However, among nonwhite females, both the crude and adjusted rates have varied appreciably. The 1953 rate was the highest for the four-year period, and the proportion of deaths ascribed to diabetes was also at a peak for the period.

The causes of death among diabetics, based upon 3,543 deaths since 1950 among patients treated at some time in the Joslin Clinic, are shown in table 6. These data relate to deaths wherever they occurred and do not represent the specific experience on such patients dying in the New England Deaconess Hospital. Most striking is the finding that fully three-fourths of the deaths were due to cardiovascular and renal conditions, and in virtually all arteriosclerosis was the underlying etiological factor. Approximately two-thirds of the deaths in this

TABLE 5
Crude and age-adjusted* death rates per 100,000 from all causes and from diabetes mellitus
United States, by color and sex, 1949-1954 (excludes Armed Forces overseas)

Race, sex and year	Crude rates		Per cent Diabetes of All causes	Age-adjusted rates		Per cent Diabetes of All causes
	All causes	Diabetes		All causes	Diabetes	
Total persons						
1954	918.8†	15.4†	1.68	771.9†	13.2†	1.71
1953	958.6	16.3	1.70	811.7	14.0	1.72
1952	961.0	16.4	1.71	817.6	14.1	1.72
1951	966.3	16.3	1.69	827.3	14.2	1.72
1950	963.8	16.2	1.68	841.4	14.3	1.70
1949	971.7	16.9	1.74	875.6	15.4	1.76
White males						
1953	1,097.7	13.0	1.18	946.5	11.3	1.19
1952	1,095.1	13.3	1.21	946.6	11.5	1.21
1951	1,098.6	12.8	1.17	955.3	11.2	1.17
1950	1,089.5	12.8	1.17	964.1	11.3	1.17
1949	1,099.0	13.2	1.20	1,000.0	12.1	1.21
White females						
1953	795.0	19.9	2.50	611.6	15.7	2.57
1952	797.1	19.9	2.50	618.4	15.8	2.55
1951	802.7	20.3	2.53	629.0	16.3	2.59
1950	803.3	20.0	2.49	645.9	16.4	2.54
1949	810.9	21.2	2.61	683.1	18.0	2.64
Colored males						
1953	1,225.0	9.8	.80	1,323.4	11.6	.88
1952	1,250.1	9.8	.78	1,344.6	11.8	.88
1951	1,249.6	10.2	.82	1,338.6	12.0	.90
1950	1,251.1	10.0	.80	1,349.8	11.6	.86
1949	1,239.4	9.3	.75	1,396.2	11.5	.82
Colored females						
1953	937.0	19.4	2.07	1,021.1	23.6	2.31
1952	960.8	18.1	1.88	1,048.8	22.2	2.12
1951	979.0	17.9	1.83	1,068.5	21.7	2.03
1950	993.5	18.7	1.88	1,087.5	22.5	2.07
1949	990.1	18.6	1.88	1,129.6	23.8	2.11

* Computed on the basis of the age distribution of the population of the United States in 1940.
† Provisional—10 per cent sample.
Source: Mortality from Selected Causes, by Age, Race and Sex. Vital Statistics—Special Reports, National Summaries, Annual Reports 1949-1953.

TABLE 6

The causes of death of diabetic patients, 1950-1955* Experience of the Joslin Clinic, Boston, Mass.

Cause of death	Number of deaths	Per cent of all causes
All causes	3,543	100.0
Diabetic coma (primary)	47	1.3
Cardio-renal vascular	2,690	75.9
Arteriosclerotic	2,666	75.2
Cardiac	1,714	48.4
Coronary and angina	1,176	33.2
Renal, total	350	9.9
Diabetic nephropathy	211	6.0
Typical or unqualified	189	5.3
Probable	22	0.6
Cerebral	470	13.3
Gangrene	66	1.9
Site unassigned	66	1.9
Other circulatory and rheumatic heart disease	24	0.7
Infections, total	193	5.4
Pneumonia and respiratory	122	3.4
Gall bladder	10	0.3
Appendicitis	4	0.1
Kidney, acute	16	0.5
Abscesses	6	0.2
Other infections	35	1.0
Cancer	367	10.4
Tuberculosis	28	0.8
Diabetes–(i.e., unknown)	22	0.6
Accidents	75	2.1
Suicides	16	0.5
Insulin reactions	7	0.2
Other diseases	98	2.8

* Deaths reported through Dec. 1, 1955.

category or nearly half of the total from all causes, were due to heart disease, and most of these were reported to be due to coronary occlusion or sclerosis. Next in order of importance in this broad category are deaths from cerebral accidents; they accounted for more than one-eighth of all the deaths. Renal conditions caused approximately 10 per cent of the total mortality, with approximately 60 per cent of these reported as diabetic nephropathy. Deaths from gangrene accounted for only 2 per cent of the total.

Among the other causes of death, malignant neoplasms stood out most prominently. In this recent experience slightly more than one-tenth of the deaths were due to these conditions. In contrast, tuberculosis accounted for less than 1 per cent of the deaths. The only other group of causes responsible for an appreciable part of the mortality consisted of pneumonia and other respiratory conditions—3.4 per cent of the total.

Primary diabetic coma accounted for a relatively small proportion of the total mortality in this recent experience —1.3 per cent of all deaths. This is the lowest figure recorded in the entire period of more than fifty years for which data on causes of death are available among patients of the Joslin Clinic. While the progress in controlling mortality from coma has been excellent, unremitting efforts to reduce deaths from this cause to a minimum should be pursued.

The Early History of The American Diabetes Association

Cecil Striker, M.D., Cincinnati

I have had the honor and privilege to have been intimately associated with the formation and early period of the American Diabetes Association. In view of the fact that I was its first President, and then its Secretary for seven consecutive years, I have had the opportunity of seeing the flourishing development of this unique organization.

Let us go back to the spring of 1939, when a small group of physicians gathered around a lunch table in New Orleans, where they had been attending the annual meeting of the American College of Physicians. A few of them had been exchanging letters as to why there was not a common meeting place for discussion by men who were interested in diabetes. A great deal of correspondence had taken place so the stage was set to create some sort of machinery to develop such an organization. It is important to record the names of Dr. Herman O. Mosenthal of New York City, Dr. Joseph H. Barach of Pittsburgh, Dr. Joseph T. Beardwood, Jr., and Dr. E. S. Dillon of Philadelphia and a few others, whose names should not be slighted but whose record is not complete. Following this meeting I met with Dr. Mosenthal to delineate specific machinery for the establishment of the American Diabetes Association. This machinery consisted of obtaining representatives from the five known existing local diabetes associations in the United States and, on April 2, 1940, the first meeting of a formal committee for the establishment of an

American Diabetes Association was held. Various committees were appointed and as a result of the activities of this initial committee a second meeting was held on June 12, 1940, in New York City. There were twenty-six physicians at this meeting. Following this, various committees were expanded and a national membership list was established. At this time it is fitting to pay great tribute to the activities of Dr. Herman O. Mosenthal, Dr. Joseph H. Barach, Dr. Joseph T. Beardwood, Jr., and Dr. William H. Muhlberg. The author is confident that, had it not been for the wise counseling of these men and their work and inexhaustible enthusiasm, the American Diabetes Association might not have been established.

The first Annual meeting of the American Diabetes Association was held on June 1, 1941, in Cleveland, Ohio. It was felt by those of us who were actively engaged in the formation of the Association that we would be most happy to have an attendance of about 250 as the program was very attractively arranged with Drs. Best, Joslin, Mosenthal and others presenting scientific papers. Much to our amazement instead of the hopeful 250, there was an attendance of over 300 physicians. This indicated to us that the progress and development of the American Diabetes Association would be assured.

In reviewing the files of the early history of the Association, one is confronted with the problem of having to omit interesting and important facts but among many important letters I wish to point out four that may be of particular interest. I quote:

UNIVERSITY OF TORONTO
Toronto 5, Canada
Department of Physiology

November 20, 1940.

Dr. Cecil Striker, President,
American Diabetes Association,
Cincinnati, Ohio.

Dear Dr. Striker:

I am very pleased to receive your letter of November 16, and I accept with a great deal of pleasure your invitation to become an Honorary Member of The American Diabetes Association.

I am keenly interested in increasing in every way possible our knowledge of the diabetic state and look forward to investigating a great many points when peace is restored. In the meantime we are able to keep a small group of workers busy in this field.

With all good wishes for the success of The Association,

Yours most sincerely,
C. H. Best
Professor of Physiology.

I would now like to quote a second letter:

UNIVERSITY OF TORONTO
Toronto 5, Canada
Department of Medical Research
Banting Institute

November 20, 1940.

Dr. Cecil Striker,
1019 Provident Bank Bldg.,
Cincinnati, Ohio.

Dear Dr. Striker:

Please accept my sincere thanks for your recent letter, for the honour that you have conferred on me in asking me to be an Honorary Member of your proposed Diabetic Association.

May I say, however, that I belong to so many organizations at the present time that I cannot contribute my share to their welfare. In addition, may I say that I have not engaged either in practice or experimental work on diabetes since 1924. For these reasons, you can readily understand that I hesitate to accept your kind offer, as I desire to get out of responsibilities rather than into added responsibilities.

Yours very truly,
F. G. Banting.

UNIVERSITY OF TORONTO
Toronto 5, Canada
Department of Medical Research
Banting Institute

December 2nd, 1940.

Dr. Cecil Striker,
1019 Provident Bank Bldg.,
Cincinnati, Ohio.

Dear Dr. Striker:

I have received your letter of November 28th, and

whereas I would again remind you that I have no right to be honoured in the manner suggested in your letter, if it would be of any assistance to you, I would lend my name, provided always that it does not involve any responsibility or work.

Yours very truly,
F. G. Banting.

I would now like to quote another letter:

The
DIABETIC ASSOCIATION
9, Manchester Square, London W. 1.

January 13, 1942.

149 Harley St.,
London, W.1.
England.

Dear Dr. Striker:

I am delighted to hear from you and the friendly contact your letter inaugurates is most welcome to our Association. They have asked me as their Chairman to convey their deep appreciation of the feelings you express and hope that our future co-operation may be close and helpful. Diabetes is universal, its progressive treatment and conquest international and calls for optimism and not sterilisation—. This sounds rather too like a Chairman, doesn't it?

My last visit (1936) to the United States was so enjoyable that the idea of another visit to your meeting in June 1942 raises fond dreams of better times. As you can imagine, a visit by myself or any of us seems impossible under present conditions but we hope your congress will still go on and be a success. Here we diabetics have had some anxious times over food and even insulin supplies, but provision and special arrangements in which our Association has been most useful, have prevented serious hardships. On the whole, diabetics have been as healthy and fit as usual and we trust the war will bring no serious difficulties to your side of the Atlantic.

I am glad to tell you that I personally am very well and busy and that life in London seems almost humdrum in its recent quiet. Our Association offices have been bombed, but our work and membership are expanding every year.

We are greatly cheered by your letter and hope our contacts may grow and expand as years go on. We are glad to be allied in every way.

With best wishes,
Very sincerely yours,
R. D. Lawrence.

One could record many human interest events in the early development of the Association. Among these, one is of sufficient interest and importance to merit special mention. Through the kind efforts of the late Dr. John R. Williams of Rochester, New York, I received this communication, which speaks for itself.

UNITED STATES MARITIME COMMISSION
WASHINGTON

December 24, 1946

Office of the Chairman

The Honorable
James W. Wadsworth
House of Representatives

Dear Congressman Wadsworth:

Subject: SS FREDERICK BANTING

This will acknowledge receipt of your letter of December 16, 1946, in which you inquire regarding the SS FREDERICK BANTING.

The FREDERICK BANTING was delivered to the British Government, under Lend-Lease, on December 30, 1943. She has since been operated by them to ports in Japan, China, Australia, India, and the Mediterranean. The most recent information in our possession reflects the fact that she left Liverpool on December 5th, bound for Halifax, N. S., and is probably now at that port.

Sincerely yours,
(signed)
W. W. Smith
Chairman

This needs no comment.

Soon after the early scientific meetings, various committees were developed. Always the interest and activities of these committees were aimed toward the benefit of the diabetic patient. The committees have studied vari-

ous problems such as quack remedies, improvements of insulin, establishment of summer camps for diabetic children, statistical investigations to ascertain more information concerning the prevalence and complications of diabetes and, in the early period of World War II, the creation of identification tags for diabetics to be used in the event of a catastrophe, and the question of establishing lay diabetes associations in which the problems of the patients could be discussed at their own meetings.

In the early days when the war was at its peak the American Diabetes Association took a leaf from the activities of The British Diabetic Association. Their experience was of great benefit to us in reference to methods of allocation of insulin, provision for emergency treatment for diabetics and the issuance of proper rations. We pay tribute and thanks to them for the lessons we learned from them.

Probably one of the greatest events in the history of the American Diabetes Association was the commemorative meeting under the joint auspices of the University of Toronto and the American Diabetes Association on September 16, 17, and 18, 1946, at Toronto, Canada, on the Twenty-fifth Anniversary of the discovery of insulin. This meeting brought together many of the leading men interested in diabetes. It was unparalleled in that the only missing members of the earlier workers in the field were Sir Frederick Banting and Professor J. J. R. Macleod. Among those in attendance were Professor C. H. Best, Professor J. B. Collip, Drs. Walter R. Campbell, A. A. Fletcher, Russell M. Wilder, Seale Harris, Elliott P. Joslin, Rollin T. Woodyatt, as well as Dr. R. D. Lawrence of London, Dr. H. C. Hagedorn of Gentofte, Denmark, and Dr. B. A. Houssay of Buenos Aires and a host of others long interested in the field of carbohydrate metabolism. This meeting attracted over 500 physicians from all parts of the world. I think it can be said that never again will it be possible to bring together a group of men so fully representative of a single field of medicine and science. It was a memorable event.

In the early history of the Association two separate publications were issued. They were *Diabetes Abstracts* and the *Proceedings*. More recently they have been combined in the Association's scientific journal DIABETES.

It should be publicly recorded that in the early development of this Association the activities of Mr. J. K. Lilly, Mr. Eli Lilly and Dr. F. Bruce Peck of Indianapolis, were of invaluable assistance. Their efforts, foresight and enthusiasm make the American Diabetes Association forever indebted to them.

So that one may have a perspective on its phenomenal growth and development it should be noted that the initial budget was $35.00 a month and I am reliably informed that in 1955-56 it totals approximately $250,000.00 annually.

The continued success and enthusiasm of the American Diabetes Association has been due to the religious devotion to service for the diabetic by its officers, Council and committees. Its present Executive Director, Mr. J. Richard Connelly, and his staff have the same devotion to service. Living testimony proves this, as there are now over 2,100 members of the American Diabetes Association from all over the world and thousands of individuals belonging to lay associations.

Any effort that was extended in the early development of this Association has been amply repaid by the service that it is giving and the distinguished position that it holds in the scientific world.

EDITORIALS

HUMORAL ANTAGONISM TO INSULIN

In the wave of enthusiasm which followed upon the discovery of insulin, it was generally felt that finally the answer to diabetes had been found. Here was a disease which resulted from a primary endocrine insufficiency and which could be treated by replacement therapy. After more than thirty years of accumulated experience in the clinical use of insulin and concomitant research in its mode of action, the extent to which this view is an oversimplification is becoming apparent. With the discovery of an increasing number of agents which interfere with or antagonize one or more of the body's responses to insulin, it has become clear that the syndrome of diabetes may result from either an absolute or a relative hypoinsulinism.

Certain of the agents which appear to antagonize insulin probably do so quite indirectly. Glucagon and epinephrine, which provoke hyperglucemia by enhancing hepatic glycogen breakdown,[1] and the so-called glucocorticoids, which cause an enhanced glucogenesis from amino acid precursors,[2] oppose the hypoglucemic effect of insulin but are devoid of any demonstrated effect upon insulin as such. On the other hand there are agents in the body which are believed to interfere with or limit the effects of insulin by chemical reaction with insulin. Among these are the proteolytic enzyme which has been named "insulinase"[3] and a component of the gamma globulin fraction of certain insulin-treated diabetic patients which behaves as though it were an antibody to exogenous insulin.[4] There is in addition evidence that some relative or derivative of growth hormone from the anterior pituitary gland in some as yet undefined fashion interferes fairly directly with certain actions of insulin.[5, 6, 7]

In the past few years there have been a number of reports of the demonstration of insulin antagonist action in the serum or plasma of certain diabetic subjects. These demonstrations have been based upon:

1. Diminution of hypoglucemic effect of insulin in the intact animal when mixed with antagonist serum.[8, 9, 10]

2. Reduction of the responses to insulin in the isolated rat diaphragm in the presence of antagonist serum.[11]

3. Decreased binding of insulin-I^{131} by diaphragm when antagonist serum is present.[12]

4. Alteration in the electrophoretic mobility of insulin-I^{131} when dissolved in antagonist serum.[4]

As far as is presently known, "insulinase" is a fixed tissue enzyme. Though abundantly present in liver homogenates, it has not been reported to occur in the blood. In at least one situation in which serum effectively antagonized the action of insulin, the presence of insulinase activity was sought in vain.[13]

Antibodies toward heterologous insulin do undoubtedly occur. The chemical basis for the fortunately mild antigenicity of insulin rests upon the demonstration that minor variations in amino acid composition of the insulin molecule, unaccompanied by significant pharmacological differences, are encountered when insulins of different species are compared.[14] The injection of pig insulin together with adjuvant into the guinea pig leads to an immunity which is in turn susceptible of passive transfer.[15]

Earlier clinical studies of insulin immunity related largely to diabetic patients who were clinically resistant to or unusually tolerant toward injected insulin.[8, 9, 10, 11] Of considerable interest was the study of a patient who required 3,000 to 6,000 units of insulin daily, whose serum was shown, in a rat hemidiaphragm technic, to be rich in antagonist activity toward insulin. Treatment with ACTH resulted in the disappearance of clinical insulin resistance and subsequently antagonist activity was found to have disappeared from the serum.[11] Although immunity to injected insulin was originally studied in the serum of insulin-resistant patients, a recent report indicates that possibly quite generally patients who have received exogenous, i.e., beef, sheep or pig insulin, develop antibodies toward these agents.[4] Since the majority of insulin-treated diabetics remain responsive to exogenous insulin it must be supposed either that the insulin-antibody complex is usually readily dissociable

or that it may retain the pharmacological action of native insulin.

Whereas the development of antibodies toward insulin may complicate the treatment of a diabetic patient, this mechanism cannot be invoked as an explanation for the etiology of diabetes unless it is shown that antibodies toward human insulin may appear in the human subject. To date such a demonstration is lacking.

One situation in which resistance or increased tolerance toward administered insulin is commonly seen occurs when the diabetic patient lapses into ketosis and acidosis. Under these conditions a patient may tolerate many times his usual daily insulin requirement and far more insulin than would be required to produce hypoglucemic convulsions in the same subject at some other time. We have recently had occasion to study sera obtained on admission from patients in diabetic acidosis, and have found insulin antagonist activity measured by the abolition of the anticipated effect of insulin on the glycogen accretion in the rat hemidiaphragm.[16] In a few patients whose requisite insulin therapy was less than 250 units in the first 24 hours, no antagonist activity could be detected by the method employed. All patients who required more than this quantity of insulin, who were therefore clinically impressively resistant to insulin, exhibited insulin antagonism in their sera. This activity is evanescent, since after as brief a period as six hours of therapy, its presence could no longer be detected. For this reason, and because the antagonist migrates electrophoretically predominantly in the *a*-globulin fraction of the serum proteins, it is believed not to be an antibody. The antagonist is nondialyzable, is not contained in the lipoprotein fraction, and is devoid of "insulinase" activity. Since this activity cannot be reproduced by injection of ACTH into a diabetic subject, it is believed not to arise in the adrenal cortex. The failure to detect this activity in the serum of an insulin-resistant diabetic acromegalic suggests that it may not be of pituitary origin, although this point will require further study.[13]

The presence of demonstrable insulin antagonist activity in the serum under a variety of circumstances emphasizes the difficulties in the development of an insulin assay procedure applicable to clinical blood samples. Without the introduction of suitable chemical separation procedures designed to free blood insulin of humoral antagonists and synergists, true blood insulin values cannot be expected from study of biological responses to blood samples. At best such assays will reveal a complex resultant of the several hyperglucemic and hypoglucemic factors known to occur in blood, of which insulin and its antagonists are representative.

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RESPIRATORY ACIDOSIS AND HYPOCHLOREMIC ALKALOSIS: ORIGINS, DIFFERENTIATION, EFFECTS AND THERAPY

The combination of an increased serum total CO_2 content and lowered levels of serum chloride may result from a primary retention of CO_2 as in cardiopulmonary disease with a secondary lowering of the chloride level, referred to as respiratory acidosis, or it may represent one of the two forms of metabolic alkalosis, i.e., the hypochloremic type stemming from losses of extracellular chloride rather than the hypernatremic type resulting from increases in serum sodium concentrations above normal.

The origins of respiratory acidosis may lie in cardiac or pulmonary disease which interferes with transfers of CO_2 across the respiratory epithelium, but can also be produced by inhalation of high concentrations of CO_2 as in asphyxia. The hypochloremic form of metabolic alkalosis can result from losses of chloride via gastric lavage, in vomitus, or in other gastrointestinal secretions, may stem from excessive urinary excretion of chloride as in patients receiving mercurial diuretics, or it may reflect, as Heppel[1] first suggested, depletion of cellular potassium. Insofar as the last category is concerned, Darrow and others[2–6] have presented evidence that as potassium moves out of cells, sodium and hydrogen move in. This results in an intracellular acidosis and an extracellular alkalosis. Under these circumstances the lowering of chloride has been interpreted as originating from dilution of chloride space, from extracellular transfers or segregation of chloride, or most likely from losses in urine. The importance of continued renal losses of potassium in the production of deficiencies of this ion have been amply established,[7–10] even though in the unstressed animal potassium conservation can be marked during periods of deprivation.[11]

In his original report Darrow and others[2] cited unpublished studies which indicated that low potassium diets unaccompanied by extra intake of sodium and chloride did not produce the marked lowering of muscle potassium, the rises in cell sodium, nor the hypochloremic alkalosis. Since then other workers have shown that significant degrees of potassium depletion, i.e., 5 per cent of the body stores, may be induced without production of either hypochloremia or alkalosis.[12,13] Abstraction of chloride, sodium loading, or interference with sodium excretion following ACTH did. Data are too limited at present to assert that hypochloremic alkalosis associated with potassium losses always represents chloride deficiency or necessitates sodium loading.

The similar and the distinguishing biochemical features of these two entities are shown in figure 1. Comparable degrees of hypochloremia and increased serum total CO_2 content may be present in both, though extremely low chloride levels, i.e., below 70 mEq/L. under these circumstances usually indicate primary chloride losses in gastrointestinal secretions. The serum *p*H which is lowered in respiratory acidosis and increased in hypochloremic alkalosis readily distinguishes between the two and, together with the serum total CO_2 content, permits calculation or estimation of the PCO_2, i.e., the partial pressure of CO_2 in serum.[14] In respiratory acidosis this value is definitely above the usual range in health (35-48 mm. Hg) and is normal or slightly increased in hypochloremic alkalosis.

Clinical signs associated with respiratory acidosis include evidences of a chronic cardiopulmonary disease, if that is its etiology, with dyspnea and cyanosis and loss of consciousness with oxygen therapy, while metabolic alkalosis may result in tetany, weakness, mental confusion and a variable degree of hypoventilation. In respiratory acidosis the urine becomes more acid. In hypochloremic metabolic alkalosis the urine is usually alkaline but may be acid, especially in potassium deficiency, presumably because this ion is not available for competition with hydrogen in exchange for reabsorbed sodium.[14]

The chief importance of these two conditions lies in the fact that they are useful indicators of profound disturbances in body fluids which require corrective therapy. In respiratory acidosis this is limited to measures designed to improve ventilatory exchange and minimize production of H_2CO_3 by inhibition of carbonic anhydrase by agents such as Diamox.[R] In hypochloremic alkalosis interruption of etiologic factors such as vomiting, ACTH or steroid therapy and replacement of chloride deficits or of potassium deficits usually suffices. HCl and NH_4Cl have been used for this purpose but involve unnecessary risks and may prove fatal in patients thought to have hypochloremic alkalosis but really suffering from respiratory acidosis.

It is to be noted that the rise in the serum total CO_2 content and the degree of hypochloremia can be identical in those two conditions. Measurements of the *p*H and an estimate of the PCO_2 as derived from nomograms[14] serve to differentiate them.

In respiratory acidosis the retention of CO_2 increases PCO_2 and hence the H_2CO_3 and H^+ of the body fluids.

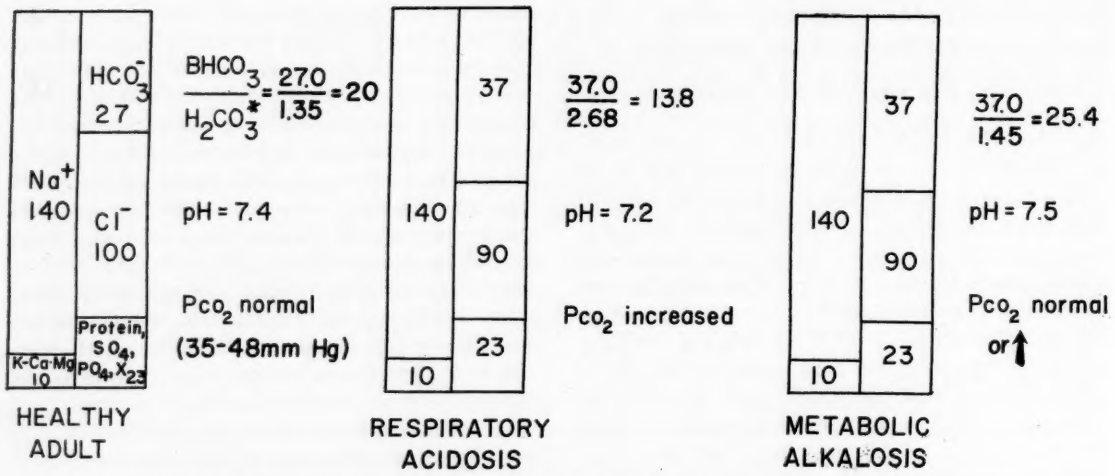

FIG. 1. Cation-anion pattern in healthy adults and in patients with respiratory acidosis or hypochloremic (metabolic) alkalosis.
By accepted and convenient convention $H_2CO_3 = K_0Pco_2 \cdot K_0$ = solubility coefficient of carbon dioxide = 0.03mM per L (plasma) per mm (mercury) Pco_2; t = 38°C. Strictly speaking, $K_0Pco_3 = CO_2$ (unhydrated) + H_2CO_3 (hydrated or true carbonic acid).

$$PCO_2 + H_2O \overset{\text{carbonic anhydrase}}{\leftrightarrows} H_2CO_3 + H_2O \leftrightarrows HCO_3^- + H_3O^+$$

The secondary lowering of serum chloride values permits an increase in the serum bicarbonate associated with cations which exerts a common ion effect upon the bicarbonate derived from H_2CO_3, driving the above reaction to the left. This is not sufficient, however, to restore *p*H values to normal and an acidosis persists.

In hypochloremic (metabolic) alkalosis the decrease in chloride permits an expansion in the bicarbonate associated with cations and, by the common ion effect, diminishes the ionization of H_2CO_3. The *p*H is therefore raised. The secondary hypopnea which may increase the Pco_2 slightly above normal usually does not cancel the change in *p*H.

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John Rollo

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In 1797 there was published in England a book entitled in part, *An Account of Two Cases of the Diabetes Mellitus*. In it John Rollo, M.D., a surgeon of the Royal Artillery, recorded in detail his observations regarding the course of diabetes in two patients treated by means of a special diet. As a result, his methods of treatment and ideas regarding the origin of diabetes were widely discussed in England and on the Continent with acceptance by some and rejection by others. Rollo has become known as the first, or certainly one of the first, to plan definite diets for diabetic patients.

Rollo was born in Scotland and received his medical education at Edinburgh. He became a surgeon in the English army in 1776 and served in the West Indies, being stationed on the island of St. Lucia in 1778 and 1779 and on Barbados in 1791. He appears to have been a man of inquiring mind with both talent and energy. As a military physician, his interest in disease was general. His account entitled *Observations on the Diseases in the Army on St. Lucia* was published in 1781. This was followed in 1785 by *Remarks on the Disease lately described by Dr. Hendy* (that form of elephantiasis so common as to be known as "Barbados leg") and in 1786 by *Observations on the Acute Dysentery*. He was advanced to the grade of Surgeon-General in 1794. In 1801 there appeared his *Short Account of the Royal Artillery Hospital at Woolwich* and in 1804 a *Medical Report on Cases of Inoculation* in which he supported the views of Jenner. Rollo died in 1809 at Woolwich, the seat of the Royal Artillery Academy and now a borough of London.[1]

A second edition of the book on diabetes was published in 1798[2] and a third in 1806. Rollo was frequently consulted regarding cases of diabetes and his book carried notes and communications regarding patients seen by other physicians who had applied his method of treatment and had written to him regarding the results. In his work Rollo had the cooperation of William Cruickshank, artillery surgeon, chemist and apothecary, who carried out studies on the quantity and nature of the sugar in urine.

Rollo's account of the circumstances under which he became interested in the treatment of diabetes reads in part as follows:[2]

"In the year 1777 . . . . I saw a case of the Diabetes Mellitus in a weaver at Edinburgh. He had been at least four months in the Royal Infirmary without having derived any advantage, and was chiefly under the care of the late Dr. Hope, Professor of Botany. When the patient was discharged, a Mr. Johnstone, then a Student of Physic, and myself, detained him a few days, and paid his expenses, in order to bleed him, and obtain some of his urine, so as to ascertain the appearances and spontaneous changes. I well remember that the blood and urine exhibited the appearances described by Dr. Dobson; but the papers, and a portion of the saccharine extract, which I carried with me abroad, were lost in the hurricane at Barbadoes in 1789.

"From that period I had not met with a case of Diabetes, although I had observed an extensive range of disease in America, the West Indies, and in England, until 1796.

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"Captain Meredith, of the Royal Artillery, being an acquaintance, I had seen him very frequently, previous to his going on camp duty in 1794, but then he had no disease; however, he always had impressed me, from his being a large corpulent person, with the idea that he was not unlikely to fall into disease. (*Editor: Another instance of Rollo's clinical acuteness.*)

"On the 12th of June, 1796, he visited me, and though I was at once struck with the diminution of his size, yet, at the same time, the colour of his face being ruddy, I received no impression, otherwise than of his being in health: a moment's conversation, however, convinced me of the contrary. . . .

"He complained of great thirst and a keenness of appetite; his skin was hot, dry and parched; and his pulse small and quick. He told me his complaints had been attributed to an old disease, and a liver affection. The thirst, dry skin, and quick pulse, marking a febrile state, depending probably on some local circumstance, and connecting these with the keenness of appetite, Diabetes immediately suggested itself to me. I enquired into the state of his urine, which I found in quantity and colour to be characteristic of the disease; and was at the same time much surprised, that for the two or three months he had been under the care of a Physician and Surgeon, the circumstance of the increased urine had not been known to them. The patient told me, as he drank so much, the quantity of urine had appeared to him a necessary consequence; and of course never having been asked about it, he gave no information. I directed him to keep the urine he next passed, and, on examination, it was found to be sweet; in consequence of which the disease became sufficiently ascertained."

At another point in the case history, Rollo states that Captain Meredith was 34 years of age and was 71¾ inches tall. At the time of beginning of the special treatment, the symptoms of diabetes had been present seven months or more and his weight had fallen from 232 to 162 pounds.

A view held by some at that time was that diabetes was a primary affection of the kidneys. However, Rollo developed the idea that the disease was "a primary and peculiar affection" of the stomach in which, due to some morbid changes in "the natural powers of digestion and assimilation," sugar or saccharine material was formed in that organ, chiefly from vegetable matter. It was on this basis that he advocated the use of an animal diet together with certain medication designed to quiet the overactive stomach and to diminish the appetite. Following initial bloodlettings, Rollo's treatment of Captain Meredith was as follows:

"1st. The diet to consist of animal food principally, and to be thus regulated:

Breakfast. One and a half pint of milk and half a pint of lime-water, mixed together; and bread and butter.

Noon. Plain blood-puddings, made of blood and suet only.

Dinner. Game, or old meats, which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork. To eat in moderation.

Supper. The same as breakfast.

"2dly. A drachm of kali sulphuratum to be dissolved in four quarts of water which has been boiled, and to be used for daily drink.

No other article whatever, either eatable or drinkable, to be allowed, than what has been stated.

"3dly. The skin to be annointed with hog's lard every morning. Flannel to be worn next the skin. The gentlest exercise to be only permitted; but confinement to be preferred.

"4thly. A draught at bed-time of twenty drops of tartarized antimonial wine, and twenty-five of tincture of opium; and the quantities to be gradually increased. In reserve, as substances diminishing action, tobacco and foxglove.

"5thly. An ulceration, about the size of half a crown, to be produced and maintained externally, and immediately opposite to each kidney. And,

"6thly. A pill of equal parts aloes and soap, to keep the bowels regularly open."

Captain Meredith began the above treatment on Oct. 19, 1796. Two days later the quantity of urine passed in twenty-four hours had fallen from seven or eight quarts to six quarts. By November 1 the quantity did not exceed four quarts and on November 4 "he drank only three pints of water, and made only two quarts of urine, which to him and his servants (who had been in the habit of tasting his urine from curiosity) was not sweet." As time went on, the opium at bedtime was discontinued and the rubbing with hog's lard was left off. The latter was found to be a "troublesome and disagreeable" part of the treatment. Rollo decided to simplify therapy to include those features which were considered really essential: animal food, confinement with limitation of activity, and hepatized ammonia. The hepatized ammonia (ammonium sulphide) was used in place of "kali sulphuratum," originally prescribed, with the thought that it might be "a more certain and active medicine than the other on the stomach, in diminishing its action."

Captain Meredith was directed to keep notes regarding his symptoms, diet, medication and progress of his illness. He did this quite faithfully, recording his transgressions as well as his attempts at cooperation. When at times he indulged in apples, bread and beer, Rollo found it necessary "to point out in stronger language the impropriety of such deviations." By December 30 the patient was free from abnormal thirst and polyuria, was regaining some of his lost weight and felt well. Continuation of treatment with a somewhat more liberal allowance of bread in the diet was prescribed.

Rollo's second case was an unnamed "General Of-

ficer," aged 57, with symptoms of diabetes dating back at least three years. His primary disease was complicated by other conditions and he was not nearly as cooperative as Captain Meredith. He died nineteen months after first being seen, having been under Rollo's direct observation for less than two months. During the last three months of his life he had returned to an unrestricted diet including apple-pudding, tea with sugar, and wine.

Rollo, with the aid of Cruickshank, carried out laboratory studies with his patients to ascertain the results of treatment and to elucidate the nature of diabetes. The fluid intake, urine output and the body weight were determined. The urine was tasted to indicate the presence of sugar and subjected to experiments before and after evaporation to determine its chemical composition and content of sugar. At the beginning of treatment when Captain Meredith was passing up to twelve quarts of urine in twenty-four hours, the following notes were made:

"Mr. Cruickshank took 36 ounces troy weight of urine voided today, and it yielded by evaporation three ounces and one drachm of saccharine extract, of the appearance of molasses, but thicker, having nearly the consistence of wax, and somewhat tenacious. If, therefore, the whole of the day's urine had been evaporated it would have yielded about 29 ounces troy weight, an astonishing quantity to be formed and separated from the system. By standing in the air it became moist, and of nearly the consistence, smell and appearance of treacle.

"Treating some of this extract with the nitrous acid, he procured the saccharine or oxalic acid; and with a smaller proportion of the acid it produced a substance, which in resemblance, and smell, could not be distinguished from honey."

From studies on blood, Rollo and Cruickshank concluded that sugar might be present without being detectable by taste and that if two or three ounces of serum from the blood of a diabetic patient were taken at a proper time after eating, it was probable that saccharine matter might be obtained. From such studies and from the finding of normal-appearing kidneys at autopsies on diabetic individuals, Rollo argued against the idea that diabetes was primarily a renal disease. Instead, he conceived of the process as follows:

"The serum of the blood apparently containing less saccharine matter than the urine, may depend on the power of the kidneys in separating it in common with the other saline matters of the blood; but proving a new and peculiar stimulus, their action is increased, and the saccharine matter consequently separated speedily and in proportion to its formation in the stomach."

In summing up and evaluating Rollo's contributions, we find among his erroneous ideas and bizarre treatment much that was good. He conceived of diabetes as being a disease of the stomach with overactivity of that organ with the secretion of an abnormal gastric juice and the formation of sugar in the stomach chiefly from foods of vegetable, as opposed to animal, origin. Hence the source of sugar formed in the stomach was to be reduced by using a diet liberal in protein and fat and restricted in carbohydrate (though milk was included provisionally under animal food). In order to quiet the stomach and reduce the appetite, drugs were given to produce anorexia and nausea. These included potassium sulphate (later ammonium sulphide), antimony, opium, tobacco and digitalis. "Fat and rancid old meats" likewise tended to discourage appetite. The end-result of Rollo's plan of treatment was an over-all restriction in calories, particularly those derived from carbohydrate. In this connection it is instructive to note that when Captain Meredith had improved and glycosuria was thought to have disappeared, Rollo in liberalizing the diet directed him to begin with the "use of cabbage, or greens of a similar nature, boiled onions, or salad without acid sauce; also mustard, horseradish, and common radish when in season."

Although Rollo's method of treatment was widely used and often enthusiastically endorsed, at least in part, by many physicians, it never gained general adoption in any country, except perhaps in England. Even there, a decline in popularity gradually took place which may be "attributed to the crudeness and imperfections in the method itself, the careless and faulty application of it by most physicians, the rebellion of patients—who generally, sooner or later, secretly or openly broke the intolerable dietary restrictions and relapsed—the failure of the method to check the severest cases, and the frequent bad results . . . . of changing diabetic patients suddenly from a mixed diet to a strict protein-fat regimen."[3] Nevertheless, Rollo's contribution to the development of knowledge regarding diabetes and its treatment was significant and has won for him lasting recognition.

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[2] Rollo, John: Cases of the Diabetes Mellitus, with the Results of the Trials of Certain Acids, and other Substances, in the Cure of the Lues Venerea, 2nd ed., London, T. Gillet for C. Dilly, 1798.

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Correspondence

PROGRESS REGARDING DIABETES IN ITALY

To the Editor:

There is a great deal more work going on in other parts of the world in the study and care of diabetes and diabetics and more interest in the disease from a sociological standpoint than we here in the United States realize. That was forcefully impressed upon me last summer in Cambridge, England, at the Second Congress of the International Diabetes Federation, and even more strikingly during the few days I spent in Rome in September 1955 substituting for Dr. Priscilla White who, temporarily indisposed, was prevented from reading her two scheduled papers. Under the aegis of the National Council of Research of the National Institute of Nutrition, this was the third conference of European scientists and physicians devoted to dietetics. It was followed by a shorter conference upon diabetes in childhood.

Les Journees de Dietetique was originally organized by Professor Charles Richet for the purpose of facilitating the meeting and exchange of ideas between nutritionists and dietitians and was organized for the first time in Paris in 1952 at L'Hôpital de la Pitie. This was followed by a second meeting in Zurich and Basle, Sept. 27-30, 1953. Although it was especially designed for those in the Latin countries, scientists from other parts of the world were welcomed.

The inauguration of the three-day meetings was held in Rome in the Palace of the National Council of Research, with subsequent meetings in the National Institute of Nutrition.

Nine papers on "Diet and the Suprarenal Glands," with discussions, occupied the first day. Six papers on "Enrichment of the Diet" were given on the morning of the second day, and "Diet for the Aged," with seventeen speakers, was presented upon the third day.

Upon the following two days, September 24 and 25, twenty papers were read upon various aspects of the clinical pathology of diabetes in childhood. Most of these papers were delivered at the Diabetarium in Santa Marinella, about thirty-seven miles from Rome and overlooking the Mediterranean.

In May 1952, Monsignor Ferdinando Baldelli asked Professor Carlo Faelli if it would be possible to organize a clinic for diabetic children and in August of that same year the Diabetarium was started. It was built and is operated under the auspices of the Pontificia Opera Assistenza. The fifty children between the ages of five and fifteen years for whom it provides come generally from the Pediatric Clinics of the Italian Universities from all parts of Italy. The parents, the cities or the provinces pay nothing, but the Italian Government (*Alto Commissariato Igiene e Sanita*) contributes about 800 lire daily for each child. Monsignor Baldelli is the president of this body and it is through him that the Pope has shown his deep interest in this project, as he has also in the *Instituto di Diabetologia e Medicina Funzionale.*

The camp children appeared in perfect health, just as do the diabetic children at our Clara Barton and Elliott P. Joslin Camps. They seemed extremely happy and were wonderfully well-behaved.

The medical care is individualized and the charts for each child show weights, intake of food and insulin. Results of daily urine tests and blood sugar tests every other day were portrayed in such a clear manner that one can trace the course of each child for months at a glance. I have never seen anything done like this so well before.

Accommodations for the children are exquisite with modern plumbing and an abundance of wash bowls and lavatories—all in scrupulously clean condition.

It was worth a trip to Italy to see Dr. Faelli's battalion of diabetics, who live in Santa Marinella all the year round, and to have the opportunity to observe the wonderful supervision the nuns give to their charges. As I understand, their education is carried on along with their medical instruction. Cardinal Tisserant, Dean of the College of Cardinals, and Monsignor Baldelli were present to greet the hundred and more doctors who visited it.

In Rome there was also another organization which does much for diabetics, taking care of hundreds of them in an outpatient department. It is called *Associazione Italiana per la Difesa Degli Interessi dei Diabetici* and the office is at Via Varsilia 2.

Professor Silvestri Lapenna, recently chosen to be one of the ten Councilors of the International Diabetes Federation, is the moving spirit. This clinic was organized some two years ago. Patients are seen by appointment day or night. Laboratory facilities are available, as well as provision for X ray. There are many conference rooms for individual interviews and classrooms for instruction. The most modern arrangements for the management of an outpatient department are available, and yet a friendly atmosphere is preserved. There is no doubt Europe has profited much by being forced to start with new equipment. Where the money came from to finance the considerable cost of maintenance of this outpatient clinic I

did not clearly learn, but I gathered the patients paid little and gifts were few. I judged the personnel—doctors, nurses, technicians—gave liberally of their own time. This venture in the treatment of diabetes in a large city is worth watching.

Would it not be helpful to all readers of DIABETES, Mr. Editor, if we could have a letter each month from members in one or more countries telling us news of what is going on in diabetes in their lands?

ELLIOTT P. JOSLIN, M.D.
Joslin Clinic
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Editor: The Editorial Board is presently considering ways and means to facilitate the wider distribution of the Journal to foreign lands and to increase contributions from foreign students of diabetes and related disorders. Newsworthy letters or general articles from abroad will be welcome.

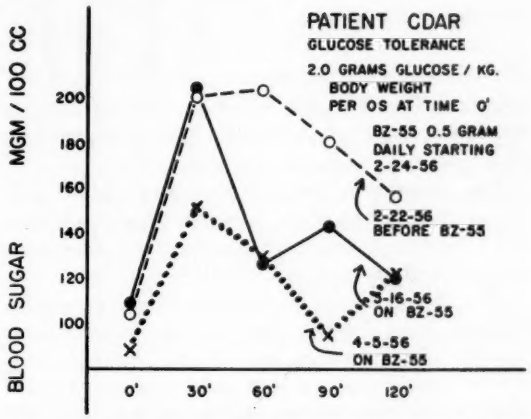

FIG. 1. Change in glucose tolerance in a juvenile diabetic. A glucose tolerance test done on May 15, 1956, was normal. The patient receives 0.25 gm. BZ-55 twice daily.

NORMALIZATION OF INSULIN TOLERANCE WITH SULFONAMIDE IN AN EIGHT-YEAR-OLD CHILD

To the Editor:

The "Insulin-Sparing-Sulfonamides" (if this proves to be the correct designation of these drugs) have several possible fields of clinical application.

It occurred to us that if they were true "insulin sparers" it might be possible, by diminishing the load upon islet cells, to postpone the onset of clinical diabetes in a child with asymptomatic glycosuria and a highly abnormal glucose tolerance curve.

Accordingly, N_1-sulfanilyl-N_2-n-butylcarbamid (BZ-55) was administered to an eight-year-old child, the son of a staff physician, whose glycosuria had been discovered some months previously in the course of a routine urinalysis. Glucose tolerance tests had been found to be grossly diabetic in type on several occasions. The results of sulfonamide administration are shown in figure 1. The data appear to be quite unequivocal. The child is in excellent health and continues to follow a diet low in concentrated carbohydrates, identical with that which he received prior to sulfonamide administration.

Only time will determine whether clinical diabetes can be permanently deferred in this child and in other similar patients. This type of observation emphasizes the importance and usefulness of detection drives designed to unearth juvenile diabetes in the preclinical phase.

Addendum: Subsequently it became necessary to reduce the dose to 0.25 gm. once daily, because of clinical hypoglycemia.

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The BZ-55 was furnished through the courtesy of Eli Lilly and Company, Indianapolis, Indiana.

BOOK REVIEWS

THE THYROID: A FUNDAMENTAL AND CLINICAL TEXT. *Edited by Sidney C. Werner, M.D., with sixty contributors. $20.00, pp. 789, 1st edition. Paul B. Hoeber, Inc., New York, N. Y., 1955.*

This well-written, authoritative book is the outstanding monograph of the many that have been written about the thyroid gland, and it probably will become the standard textbook in its field.

The subject material is divided into three main parts. Part one is an excellent description of the microscopic anatomy, the physiology, and the biochemistry of the normal thyroid gland, as well as the relationship of the gland to the hypothalamus and to the thyrotropic hormone from the pituitary gland. Part two is a practical interpretation of the basal metabolic rate, the serum-precipitable iodine and the newer butanol-extractable iodine determinations in relation to thyroid function and dysfunction. Also, there is discussion of the physical aspects of the use of radioiodine, of instrumentation and the various clinical radioiodine procedures. Part three, comprising two-thirds of the text, describes the various diseases of the thyroid gland. There are chapters on thyroid embryogeny, surgical anatomy, pathology of the various diseases and of the nontoxic goiter. Particularly worth while are the sections on physical examination of the thyroid, surgical and radioiodine treatment of thyroid cancer, clinical symptoms and signs of hyperthyroidism, hypothyroidism, and acute nonsuppurative thyroiditis. Also, there are three pages describing the association of diabetes and hyperthyroidism. Dr. Francis Lukens points out in this discussion that uncontrolled diabetes mellitus per se may elevate the basal metabolic rate as well as clinically simulating hyperthyroidism.

The reviewer believes that most of the information in this first edition is representative of the beliefs of most other authorities in the field of thyroid diseases. The one major exception to current views is the concept of the nature of the true toxic nodular goiter. Exception may well be taken to the following statements:

> Toxic nodular goiter is resistant to all forms of therapy including surgery.
>
> Recurrence (of hyperthyroidism) after subtotal thyroidectomy may be more common in toxic nodular than in toxic diffuse goiter.
>
> Toxic nodular goiter, in turn, has two variants: a relatively rare one in which a single hyperfunctioning nodule is the source of trouble (correct), and the other in which the parenchyma of the thyroid is hyperactive and the contained nodules presumably are those of coincidental nontoxic nodular goiter.
>
> Severe eye changes have followed surgical and radioiodine treatment of true toxic nodular goiter.

Most clinicians experienced in thyroid disease agree with H. S. Plummer's view that the hyperthyroidism in true toxic multinodular goiter is due to an activity of one or more nodules, and which has been shown by radioiodine scintigrams usually to be due to one hyperfunctioning nodule. It is not associated with eye signs unless the hyperthyroidism is due to Graves' disease with hyperplasia of internodular thyroid parenchyma. Also, true toxic nodular goiter is readily and effectively treated by surgery with a rate of recurrence of less than one-half per cent.

Moreover, this reviewer cannot agree with the statement:

> Measurement of the cholesterol has therefore been utilized as an aid to the diagnosis of hypothyroidism, but has proved unreliable for much the same reasons that have discredited it as a diagnostic aid in a number of other diseases.

While the serum cholesterol test has its limitations it is still a useful aid in the diagnosis of hypothyroidism.

Despite these very few limitations it is to be highly recommended as a source book, especially for the general internist, the endocrinologist, and the thyroid surgeon.

FUNDAMENTALS OF BIOCHEMISTRY IN CLINICAL MEDICINE. *By Niels C. Klendshoj, M.D., Assistant Professor of Pathology, Director of the Division of Toxicology, University of Buffalo School of Medicine, Buffalo, New York. $7.75, pp. 279, Charles C Thomas, Springfield, Illinois, August, 1953.*

The author of this volume is Director of the Department of Biochemistry at the Buffalo General Hospital and holds appointments in Pathology and in Toxicology at the University of Buffalo School of Medicine. In the work, atomic and molecular structure, acid-base balance, body fluids, carbohydrate, fat, protein, nutrition, the liver, kidney, the nervous system and each of the endocrines are discussed in individual chapters. Structural formulae are frequent (unfortunately errors are present in some of them), but this is not a text on laboratory methods nor in clinical biochemistry. Selected references varying in number from 2 to 23 are presented at the end of each chapter. The index consists of approximately 800 entries.

The wide range of subjects covered in limited space permits a quick but necessarily superficial review of the biochemistry which underlies many aspects of clinical medicine.

ABSTRACTS

Anderson, George E. (Brooklyn Hosp. and State Univ. of New York, Coll. of Med., New York, N.Y.): THE DIABETIC PROBLEM. Pennsylvania M. J. *59*:317-22, March 1956.

Allow insulin and its normal economy to lead the way to new vistas of therapeutic accomplishment. Its correct use demands that physiology replace the present empiricism in its exhibition. The future hope for the diabetic would seem to depend on establishing a more normal groundwork on which to build a sound physiologic rather than an artificial improvement.

Baker, R. W. R.; Joiner, C. L.; and Trounce, J. R. (Diabetic Clin. and Depts. of Chem. Path. and Med., Guy's Hosp., London, England): A STUDY BY PAPER ELECTROPHORESIS OF THE SERUM-LIPOPROTEINS IN DIABETIC AND NONDIABETIC SUBJECTS. Quart. J. Med. *24*:295-305, October 1955.

The lipoprotein patterns of 80 patients with diabetes mellitus and 50 nondiabetic subjects have been studied, with particular reference to the ratio between the *B* and *a* bands. It is concluded that the *B/a* lipoprotein ratio is significantly higher in diabetic patients in general and in diabetics with clinical evidence of atheroma than in diabetics without such evidence. The degree of control in the younger diabetic and the presence or absence of obesity in the older diabetic appear to be the chief factors associated with a high *B/a* lipoprotein ratio.

Baron, D. N. (Royal Free Hosp. Med. Sch., London, England): HYPOTHYROIDISM AND DIABETES MELLITUS. Lancet *2*:796-98, Oct. 15, 1955.

The author reports on four patients with diabetes mellitus among ninety-one cases of hypothyroidism. The carbohydrate tolerance improved during myxedema. A review of the literature is given.

Bauer, Heinz; Ajello, Libero; Adams, Elizabeth; and Hernandez, Domingo Useda (Depts. of Path., Emory Univ. Sch. of Med., Emory Univ. Hosp., Grady Memorial Hosp., and Dept. of Health, Educ. and Welfare, Communicable Disease Center, Public Health Service, Chamblee, Ga.): CEREBRAL MUCORMYCOSIS: PATHOGENESIS OF THE DISEASE. DESCRIPTION OF THE FUNGUS, RHIZOPUS ORYZAE, ISOLATED FROM A FATAL CASE. Am. J. Med. *18*:822-31, May 1955.

Two patients with diabetes mellitus who died of cerebral mucormycosis, an unusual and generally fatal complication of diabetes mellitus, are reported. In one patient, the disorder was suspected ante mortem, and appropriate cultures and tissue samples were obtained. *Rhizopus oryzae* were isolated and identified as the infectious agents. The clinical and autopsy findings of this fungus disease in the authors' and previously reported cases are reviewed. The paranasal sinuses are suggested as a possible portal of entry of the infection. They suggest that the disease may be recognized ante mortem by the syndrome of uncontrolled diabetes mellitus associated with ophthalmoplegia, signs of meningoencephalitis, and, possibly, sinusitis.

Bell, Joseph L.; and Barnett, Gordon J. (Mental Hygiene Unit, Veterans Hosp., New York Regional Office, New York, N. Y.): INTENSIVE INSULIN SUB-COMA TREATMENTS COMBINED WITH GROUP THERAPY IN A MENTAL HYGIENE CLINIC. Dis. Nerv. System *16*:80-85, March 1955.

The authors have treated 40 psychoneurosis and 32 schizophrenia patients with insulin sub-coma dosages. Sixty-nine per cent were markedly or moderately improved.

Beloff-Chain, Anne; Catanzaro, R.; Chain, E. B.; Masi, I.; Pocchiari, E.; and Rossi, C. (Laboratorio di Chimica Biologica, Instituto Superiore di Sanità, Rome, Italy): THE INFLUENCE OF INSULIN ON CARBOHYDRATE METABOLISM IN THE ISOLATED DIAPHRAGM MUSCLE OF NORMAL AND ALLOXAN DIABETIC RATS. Proc. Roy. Soc., London, s. B *143*:481-503, May 1955.

The fate of uniformly labeled C^{14}-glucose in the isolated diaphragm muscle of normal and alloxan-diabetic rats has been studied by a quantitative application of the radioactive paper chromatography technic. No significant differences were observed in the metabolism of glucose by muscle from normal and diabetic rats. About 80 per cent of the glucose metabolized by the extra glucose which disappeared from the incubation medium in the presence of insulin was found to be incorporated in oligosaccharides and polysaccharides; the percentage of glucose converted into the other main metabolites (i.e., lactic acid, hexose-phosphate esters, and CO_2) were unchanged or decreased by insulin. Insulin markedly accelerated the synthesis of oligosaccharides and polysaccharides. The amount of free glucose in the tissues, which reached a maximum after 15 minutes of incubation, was influenced by insulin. When the muscle was first incubated with C^{14}-glucose in the absence of substrate, there was a sharp decrease in the radioactivity of all the intermediates, with the exception of the hexose-

phosphate esters, which were found to accumulate.

Under anaerobic conditions, the total glucose metabolism was very reduced, and the greater part of the glucose which disappeared from the medium was recovered as free glucose in the tissues. Very little radioactive lactic acid was formed under anaerobic conditions, except when the muscle was first incubated with C^{14}-glucose aerobically and then anaerobically; under these conditions there was a considerable accumulation of radioactive lactic acid.

These findings could not be accounted for by the authors in terms of the hypotheses that insulin acts either to increase cell permeability to glucose or to accelerate the hexokinase reaction within the cell.

Beyer, Robert E. (Dept. of Biology, Brown Univ., Providence, R. I.): A Study of Insulin Metabolism in an Insulin Tolerant Strain of Mice. Acta endocrinol. *19*:309-32, August 1955.

The mechanism which affords a strain of mice (KL) high insulin tolerance has been studied. It has been found that the carbohydrate metabolism of the insulin tolerant mouse reacts normally to the administration of insulin. For example, diaphragms of KL and Lt (control) mice did not differ in their ability to consume glucose and synthesize glycogen either with or without the stimulus of in vitro insulin. Upon the injection of insulin into these strains, the blood glucose level falls and the muscle glycogen level rises. The point of difference between these two strains seems to be their ability or inability to recover from these changes in carbohydrate levels. The liver of the insulin tolerant mouse apparently contains an enzyme, labeled insulinase, which displays an in vitro activity great enough to account for the inactivation of the 200 to 300 units of insulin which are injected into these animals. In the KL animal this high concentration of insulinase is confined to the liver. A suggestion is presented that insulinase destroys excess insulin injected into the KL mouse, thus enabling the compensatory reactions of the adrenal hormones to become effective. The possible role of an insulinase inhibitor as a competitor against insulin for active groups on the insulinase molecule is discussed.

Bogoch, A.; Casselman, W. G. B.; Kaplan, A.; and Bockus, H. L. (Depts. of Med. and Gastroenterol., Grad. Hosp., Univ. of Pennsylvania, Philadelphia, Pa., and Banting and Best Dept. of Med. Res., Univ. of Toronto, Toronto, Canada): Studies of Hepatic Function in Diabetes Mellitus, Portal Cirrhosis and Other Liver Diseases. A Correlation of Clinical, Biochemical and Liver Biopsy Findings. I. Diabetes Mellitus. II. Portal Cirrhosis and Other Liver Diseases. Am. J. Med. *18*:354-84, 1955.

The clinical and biochemical findings were correlated with histologic and histochemical observations on liver tissue obtained by needle biopsy in 16 patients with diabetes mellitus, 7 with portal cirrhosis but no diabetes, and 10 with other liver diseases. Blood and liver tissue studies were performed simultaneously. Among some of the diabetic patients, abnormalities of serum protein and bromsulfalein retention were noted frequently; abnormalities in the turbidity and flocculation tests, infrequently. Focal lesions, considered to be of necrotic origin, and degenerative changes in the parenchymal cells occurred in 16 of the 19 diabetic patients. Similar lesions were also found in the livers of 3 of the 7 patients with portal cirrhosis and 6 of the 10 with other liver diseases. Therefore, they were not considered to be characteristic of the diabetic state.

During the accumulation of lipids in the diabetic liver, the neutral fats were most extensively involved. No correlation could be established between the degree of fatty metamorphosis of the liver and other histochemical or laboratory observations. Among the diabetic patients, there was a suggestive correlation between marked increases of lipids and hepatomegaly. Intranuclear glycogen, which gave rise to vacuolation or "ballooning," occurred to some degree in 13 of the 16 diabetic patients, in 1 of the 7 with portal cirrhosis, and in 4 of those with various other liver diseases. The reciprocal relationship between the amounts of nuclear and cytoplasmic glycogen reported to occur in diabetic patients was confirmed.

No relationship was found to exist between the amounts of histochemically demonstrable liver lipids and the blood lipid levels or between the liver glycogen and blood sugar concentrations.

Bohan, Edward M.; Serino, Girard S.; and Olivere, Peter J. (Depts. of Med. and Metabolism, Surg., and Radiology, St. Francis Hosp., Wilmington, Del.): Diabetes Mellitus, Pancreatic Cyst, and Low Salt Syndrome. Delaware M. J. *27*:276-81, November 1955.

A patient with indigestion for four years and diabetes mellitus for twelve years suddenly developed acidosis and a sharp pain in the lower left chest. The acidosis was corrected, but she persisted in running a low-grade temperature. A mass was palpated in the upper left epigastrium. Operation revealed a huge cyst, probably a pancreatic pseudocyst. The patient had a stormy postoperative course. Low-salt syndrome developed, together with severe postoperative shock. The medical and surgical treatment of the case are described in detail.

Breidahl, Harold D.; Priestley, James T.; and Rynearson, Edward H. (Sect. of Surg. and Sect. of Med., Mayo Clin. and Mayo Found., Rochester, Minn.): CLINICAL ASPECTS OF HYPERINSULINISM. J.A.M.A. *160*:198-204, Jan. 21, 1956.

Hyperinsulinism is a term reserved for patients who have a hyperfunctioning tumor of the islets of Langerhans or who have received an excessive amount of insulin. It is an uncommon condition. Sugar tolerance curves are of no value in its diagnosis, but fasting from a few hours to 72 hours is of great value. Any patient with true hyperinsulinism should undergo surgical exploration to search for an insulin-producing tumor of the pancreas. Its early recognition and removal may be lifesaving. This study is based on 91 patients with hyperinsulinism, in 76 of whom tumors were found. Tumors were not found in some of the remaining 15 patients.

Clarke, D. W. (Dept. of Physiology, Univ. of Toronto, Toronto, Canada): THE EFFECTS OF ADRENICAL CORTICAL EXTRACTS UPON CARBOHYDRATE METABOLISM WHEN MEDIUM COMPOSITION IS ALTERED. Canad. J. Biochem. & Physiol. *33*:845-48, September 1955.

The action of adrenal cortical extract upon glucose uptake and glycogen synthesis in the excised rat diaphragm was studied in three different media. The greatest inhibition caused by the adrenal cortical extract upon the above processes was observed when the medium contained both sodium and potassium ions. In media which contained either of these alone as the major cation, there was no significant inhibition.

Conference on Diabetes and Pregnancy: THE USE OF HORMONES IN THE MANAGEMENT OF PREGNANCY IN DIABETICS. REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR CONFERENCE ON DIABETES AND PREGNANCY. Lancet *2*:833-36, Oct. 22, 1955.

The council reports on the use of hormone therapy (oral stilbestrol and ethisterone) in 76 pregnant diabetics, with another 71 patients receiving no hormone therapy as a control group. Although different hospitals participated in the study, comparable groups were utilized. The frequencies of stillbirth and neonatal death were 24 and 26 per cent respectively; those of malformations, 4 and 7 each per group respectively. The incidences of hydramnios, edema, and albuminuria were equal in each group. The patterns of hormone excretion were similar. It is concluded that these hormones have no beneficial effect on pregnancy in diabetes.

Council on Pharmacy and Chemistry: LENTE INSULIN. J.A.M.A. *159*:34-35, Sept. 3, 1955.

Lente insulin is a sterile suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride. It is a mixture of minute particles consisting of approximately 70 per cent crystalline zinc insulin and 30 per cent amorphous zinc insulin, each of which has a sufficiently high zinc content to make the mixture relatively insoluble at the *p*H of the blood. The proportion of the components provides an antidiabetic action that is intermediate in time between that of unmodified (regular) insulin and that of protamine zinc insulin. The time of action of Lente insulin so closely approximates that of the modified protamine zinc insulin, isophane (NPH) insulin, that they can be used interchangeably. The onset of action of Lente insulin is sufficiently prompt to control the after-breakfast rise in blood sugar, and its duration of activity is usually adequate to maintain blood sugar levels during fasting without the need for supplementary injections. Lente insulin, which contains no foreign modifying protein, cannot possibly produce local sensitivity reactions attributed to protamine or globin.

Current Comment (Sydney, Australia): DIABETES. M. J. Australia *2*:815-16, Nov. 12, 1955.

The development of premature arteriosclerosis in diabetics has been the subject of controversy for many years. J. W. Headstream and J. T. Wortham hold that altered adrenal cortical function may well be responsible for arteriolar degeneration, i.e., that high blood sugar levels cause stimulation of the adrenal cortex; moreover, that insulin hypoglycemia, relative or absolute, is also stimulating to the adrenal cortex; and that the wide fluctuation in blood sugar levels in diabetics causes corresponding fluctuation in adrenal cortical secretion, especially when the long-acting types of insulin are used. These workers accordingly performed bilateral total adrenalectomy on seven patients with severe diabetes and advanced vascular disease, maintaining them thereafter with suitable doses of cortisone. Two patients showed considerable general improvement, two showed some improvement, and three died—one of adrenal insufficiency after initial improvement, one of cerebral vascular disease and progressive renal failure, and one for no stated reason after a period of slight improvement. In every instance, less insulin was required postoperatively to control the diabetes. It would seem that the treatment is justifiable in the presence of severe and progressive vascular deterioration, provided that it is carried out before the vascular changes have gone too far.

Current Comment (Sydney, Australia): FRUCTOSE. M. J. Australia 2:815, Nov. 12, 1955.

In the presence of glucose, the brain cannot adequately utilize fructose, which does not prevent hypoglycemic symptoms. The position in regard to muscle is somewhat doubtful. At best, fructose utilization by muscle is slow. Experiments have shown that, in the presence of equal concentrations of glucose and fructose, the rat diaphragm metabolizes six to seven times more glucose than fructose in the formation of glycogen and about three and a half times more glucose than fructose in the conversion to carbon dioxide and water. Fructose tolerance is greatly decreased in extensive liver damage, but this is a late manifestation. The metabolism of fructose in diabetic persons has frequently been studied, and it has been demonstrated that tissues from diabetics utilize fructose at nearly normal rates. When fructose is administered intravenously, a much larger portion of the administered sugar may be expected to enter the liver cells than in the case of glucose. This may explain the greater protein-sparing action of fructose and the favorable effect of fructose in some hepatic intoxications. The rapidity of uptake of fructose by the liver indicates its use as a substitute for glucose whenever a sugar must be administered rapidly and whenever the renal threshold for glucose is exceeded, leading to glucose wastage. Fructose can be useful during the first hours of treatment of diabetic acidosis, for it takes some time before insulin administration affects the deranged glucose metabolism in the liver, whereas fructose acts immediately. It is still uncertain whether fructose has any useful place in long-term therapy of diabetes. The administration of large amounts of fructose may have certain clinical dangers. It is not justifiable to assume that the liver will convert enough fructose to glucose to supply the needs of brain and muscle, which themselves cannot adequately utilize fructose. In patients receiving insulin and fructose, the rate of removal of glucose from the blood stream may exceed the rate of glucose formation from fructose; dangerous hypoglycemia may result, masked in the blood sugar estimations by the fructose, which reacts in the estimations exactly as does glucose. Because of the rapid metabolism of fructose when large doses are given intravenously, sufficient lactates and pyruvates may accumulate to cause significant acidosis.

Dewees, Robert L. (Memorial Hosp., Delaware Hosp., and St. Francis Hosp., Wilmington, Del.): INSULIN RESISTANCE: A CASE REPORT. Delaware M. J. 27:281-84, November 1955.

The management of the insulin-resistant diabetic patient requires only that he be given enough insulin. There is probably no such thing as absolute refractoriness to insulin, since all the patients responded when enough insulin was given. Such patients should be exceedingly cautious of insulin reactions, since sensitivity to insulin may return suddenly at any time, as is demonstrated by the case herein reported. It is significant that in most cases of extreme resistance to insulin, the resistance subsides spontaneously, although this transition may take from months to years. It is important to achieve as good control of the diabetes as is practicable, since this may well play a part in bringing about improvement.

Ditzel, Jørn; and White, Priscilla (Baker Clin. Res. Lab., New England Deaconess Hosp., and Joslin Clin., Boston, Mass.): CENTRAL RETINAL VEIN OCCLUSION IN JUVENILE DIABETES: CASE REPORT WITH CONSIDERATION OF THE PATHOGENIC RELATIONSHIP BETWEEN DIABETIC RETINOPATHY AND RETINAL VEIN OCCLUSION. J. Chronic Dis. 3:253-62, March 1956.

Though clinically diabetic retinopathy and central retinal vein occlusion are two definitely distinguishable entities, they have, when the processes are once started, many ophthalmoscopic features in common. The onset of the central retinal vein occlusion is sudden, and the time interval from onset to the development of the characteristically ophthalmoscopic picture is short. The onset and progress of diabetic retinopathy in young diabetics is slower than that of central retinal vein occlusion and occurs usually after a history of diabetes of ten years or more. However, the pattern of development from the early into severe stages is somewhat similar to that occasionally seen in cases of central retinal vein occlusion. The similarities between central retinal vein occlusion and diabetic retinopathy are not confined to the ophthalmoscopic picture but become even more striking when studied histologically. Capillary microaneurysms, the characteristic lesions in diabetic retinopathy, have likewise repeatedly been demonstrated in cases of retinal vein occlusion. The mechanism of formation of microaneurysms in retinal vein occlusion appears fairly clear. In this condition, a sudden onset of stasis occurs, which might be brought about by various factors. The stasis causes anoxia and undernutrition of the venular and capillary walls, leading to focal mural degenerative changes of the basement membrane and aneurysm formation. The production of capillary microaneurysms in diabetes may be explained in a similar way. Thus, it appears that the diabetic retinopathy and retinal vein occlusion in young diabetics has stasis in the venous retinal circulation as a common pathogenic factor. This may explain the occurrence of central retinal vein occlusion in young diabetics.

Editorial (London, England): SECOND THOUGHTS ON GLUCAGON. Lancet *2*:912-13, Oct. 29, 1955.

Comments are made on the physiology of glucagon. Though it was thought at first to be a product of the pancreatic alpha cells, the experiments of Goldner with cobalt are not compatible with this concept. The idea of glucagon as an insulin antagonist also seems to be disproved by recent work. The place of glucagon in human physiology remains unsettled.

Fabrykant, Maximilian (Dept. of Med., New York Univ. Post-Grad. Med. Sch. and Univ. Hosp., New York, N. Y.): THE PROBLEM OF FUNCTIONAL HYPERINSULINISM OR FUNCTIONAL HYPOGLYCEMIA ATTRIBUTED TO NERVOUS CAUSES. 1. LABORATORY AND CLINICAL CORRELATIONS. Metabolism *4*:469-79, November 1955.

The present study revealed that the accepted laboratory criteria of neurogenic hypoglycemia are not always found in patients so diagnosed and that the usually described laboratory and clinical features are not limited to this condition. It may therefore be concluded that functional hyperinsulinism, or functional hypoglycemia, attributed to neurogenic dysfunction, is not a distinct disease entity but rather a symptom-complex which embraces various types of spontaneous hypoglycemia associated with personality disorders as well as various clinical conditions in which hypoglycemia may represent only an incidental finding.

Fabrykant, Maximilian (Dept. of Med., New York Univ. Post-Grad. Med. Sch. and Univ. Hosp., New York, N. Y.): THE PROBLEM OF FUNCTIONAL HYPERINSULINISM OR FUNCTIONAL HYPOGLYCEMIA ATTRIBUTED TO NERVOUS CAUSES. 2. DIETARY AND NEUROGENIC FACTORS. DIAGNOSTIC AND THERAPEUTIC SUGGESTIONS. Metabolism *4*:480-90, November 1955.

A study of oral glucose tolerance tests after preliminary low-carbohydrate diets revealed: (1) that the hyperglycemic effect of such diets may be limited to the first three hours of the test; (2) that such diets do not prevent a drop of blood glucose to subnormal values in the further course of the test; and (3) that on occasions the magnitude of blood glucose depression after carbohydrate restriction may exceed that in control tests done after standard high-carbohydrate diets. Dietary management *alone* does not insure complete recovery of patients suffering from spontaneous hypoglycemia in association with personality disorders and autonomic imbalance. An outline of useful diagnostic and therapeutic measures in patients with manifestations which conform to the accepted pattern of neurogenic hypoglycemia is presented.

French, E. B.; and Kilpatrick, R. (Dept. of Med., Univ. of Edinburgh, Eastern Gen. Hosp., Edinburgh, Scotland, and Dept. of Pharmacol. and Therapeutics, Univ. of Sheffield, Sheffield, England): THE ROLE OF ADRENALINE IN HYPOGLYCAEMIC REACTIONS IN MAN. Clin. Sc. *14*:639-51, November 1955.

The clinical features of hypoglycemia have been studied in normal and hypertensive subjects and in patients after splanchnicectomy with particular reference to changes in the circulation and in white blood cells. Adrenaline output in the urine increased tenfold after insulin administration in hypertensive subjects but was unchanged in patients after splanchnicectomy. It is concluded that adrenaline is not responsible for the majority of the clinical features of acute hypoglycemia.

Führ, Jürgen; Kaczmarczyk, Jósef; and Krüttgen, Claus-Dietrich (Hauptlaboratorium des Allgemeinen Krankenhauses Ochsenzoll, and II, Medizinische Klinik des Allgemeinen Krankenhauses Barmbeck, Hamburg, Germany): SIMPLE COLORIMETRIC METHOD FOR DETERMINATION OF INULIN IN KIDNEY CLEARANCE EXAMINATIONS IN (PATIENTS WITH) HEALTHY METABOLISM AND IN DIABETICS. Klin. Wchnschr. *33*:729-30, Aug. 1, 1955.

A simple colorimetric method for determination of inulin for inulin clearance examinations with anthron reagent is reported. Through heating to 55° and 100°C., glucose and inulin can be determined side by side in the same reaction mixture. The method is equally suited for inulin clearance in persons with healthy metabolism and in diabetics with disturbed metabolism. (German)

Futcher, P. H.; and Marcus, D. M. (Dept. of Med., Johns Hopkins Med. Sch. and Hosp., Baltimore, Md.): HYPERGLYCEMIA AND GLYCOSURIA AFTER INGESTION OF GLUCOSE BY AMBULATORY PATIENTS OVER 40 YEARS OF AGE. J. Chronic Dis. *3*:294-300, March 1956.

In order to identify subjects in whom there is minor impairment of the ability to metabolize glucose, the authors employed the Folin-Wu technic to measure the venous blood sugar two hours after the ingestion of 100 gm. of glucose. During the course of diagnostic studies of ambulatory patients, 180 subjects aged 40 years or more were examined who manifested no sugar in the fasting urine and whose fasting blood sugar level was below 120 mg. per cent. In 56 (31 per cent) of the 180 subjects, the blood sugar level two hours after the ingestion of the glucose exceeded 119 mg. per cent; in 29 of these 56 subjects, it exceeded 139 mg. per cent. Following the ingestion of glucose, elevation of the blood sugar above the accepted normal value frequently occurred without concomitant glycosuria. Of these subjects in whom abnormal elevations of postprandial blood

sugar levels were thus demonstrated, a greater proportion were overweight than was the case with those in whom the levels were normal. It is suggested that subjects identified by this screening test as manifesting possible impairment of carbohydrate metabolism are subjects appropriate for repeated observation for further evidence of mild diabetes mellitus.

Gambassi, Gino; Maggi, Viviana; and Matarazzo, Carlo (Med. Clin., Univ. of Ferrare, Ferrare, Italy): CONCERNING THE PROBLEM OF THE HEPATIC INACTIVATION OF INSULIN IN VIVO. Acta med. scandinav. *153*: 201-09, Jan. 20, 1956.

The administration of insulin in high doses into the portal vein does not cause a corresponding serious hypoglycemia. In the hepatic plasma, the maximum effect of insulin on the glycogenosynthesis of rat's diaphragm can be noticed only half an hour after the administration of the hormone, then it gradually decreases; whereas the capacity of the erythrocytes of lessening the glucose rate of the medium after incubation proves to have an opposite trend. Sixty or 90 minutes after administration of the hormone into the portal vein, the living slices of the kidney and of the diaphragm have a particular glycogenosynthetic activity in contrast with those of the liver, which, having nonglycogenosynthetic activity, causes quite an opposite effect. (French)

Giffin, Eleanor; and Cortesi, Joseph B. (Diabetic Unit, Med. Dept. Ellis Hosp., Schenectady, N. Y.): CONTROL OF DIABETES. New York J. Med. 55:1858-63, July 1, 1955.

The authors have attempted to correlate the degree of control with the development of degenerative lesions in the kidney, retina, and blood vessels and other complications in a group of 46 young patients whose diabetes began between the ages of 17 months and 20 years and had been in existence from 5 to 28 years. The incidence and severity of retinopathy and nephropathy are stated to be greater in the poorly controlled than in the fair, good, or excellently controlled groups. They conclude that, in their study, control was more important than duration or severity of the diabetic state in preventing degenerative lesions.

Givner, Isadore (New York, N. Y.): OCULAR OBSERVATIONS ON THE DIABETIC PATIENT. Am. J. Ophth. *41*:285-88, February 1956.

In most cases, we are ignorant as to why the vascular system is affected; therefore, we do not know why we have retinal and vitreous hemorrhages. It is true that we can alter capillary fragility by the administration of agents such as rutin and vitamin P, but all have seen hemorrhages occur when the capillary fragility was normal. However, one should bear in mind that hypoglycemic reactions, even though of minor symptomatology, can and do produce ocular hemorrhages as well as cerebral hemorrhages in diabetic patients with retinal vascular diseases. In most cases, the so-called "brittle diabetes" cannot be controlled well enough to obviate these reactions altogether; but in other cases, it cannot be too strongly emphasized that a blood sugar of 140 mg. is of less danger than one of 60 mg. from the eye standpoint, for with hypoglycemic reactions often come retinal and vitreous hemorrhages. The ophthalmologist is in a unique position to pick up early cases of diabetes. The fundus may be normal; but if myopia increases or hyperopia decreases with no apparent cause in an individual over the age of 21 years, particularly if he has a family history of diabetes, a blood sugar is indicated. It is a good policy not to prescribe glasses under these circumstances until this test is done; you will be amply rewarded over the years for instituting this simple procedure. The most optimistic ray in the clouded sky of therapy in regard to ocular pathology is the reversibility of much retinal pathology. Frequently, one will see cases that stop progressing; the hemorrhages and exudates absorb until the patient has a reasonably normal-looking eye. A common denominator in these cases has not yet been found.

Goodman, Joseph I. (Cleveland Heights, Ohio): CAUSES OF LABILE DIABETES: ITS TREATMENT. Am. J. Med. *18*:448-53, March 1955.

The author discusses the favorable results obtained in twenty-five young "labile" diabetic patients by his method of treatment, with particular emphasis on the type of insulin employed and the mode of its administration.

Harris, Harold J. (New York, N. Y.): BRUCELLOSIS AND DIABETES MELLITUS. THE INFLUENCE OF CHRONIC BRUCELLA INFECTION AND/OR ALLERGY ON PANCREATIC FUNCTION. New York J. Med. 55:1183-85, April 15, 1955.

The incidence of chronic brucellosis and that of the diabetic syndrome are discussed. The author concludes that the coexistence of brucellosis and diabetes in some instances may be more than coincidence, since the diabetic syndrome may be reversible through treatment of the *Brucella* infection or allergy by *Brucella* antigen, alone or combined with antibiotics.

Hollifield, Guy; Parson, William; and Crispell, K. R. (Dept. of Internal Med., Univ. of Virginia Sch. of Med., Charlottesville, Va.): STUDIES OF FOOD DRIVE AND SATIETY IN MICE WITH GOLD THIOGLUCOSE-INDUCED OBESITY AND THE HEREDITARY OBESITY-DIABE-

TES SYNDROME. Metabolism *4*:537-41, November 1955.

The mechanism by which gold thioglucose produces obesity in mice is unknown. The evidence, thus far, that gold thioglucose causes damage to the hypothalamic feeding center is limited to similarities of response to food manipulation on the part of gold-obese mice and rats with electrolytic lesions of the hypothalamus which produce hyperphagia and obesity. Mice with gold thioglucose-induced obesity do not respond to starvation with increased running activity, nor do they show a decrease in this activity on refeeding as do normal mice. This does not appear to be due to obesity per se. Mice with congenital obesity respond to starvation in the same fashion as do normal mice. Their response to refeeding is not as striking as that of normal mice. This suggests that mice with gold thioglucose obesity do have a defect in the central food-drive mechanism and a greater defect in the satiety mechanism.

Hugh-Jones, P. (University College of the West Indies, Jamaica): DIABETES IN JAMAICA. Lancet *2*:891-97, Oct. 29, 1955.

Observations were made on 215 diabetic patients in Jamaica. They could be grouped according to Himsworth's Types I and II. However, thirteen were unusual in that they were young, thin, insulin-resistant, and free of ketosis. Management is difficult because of social conditions.

Izzo, Joseph L.; and Eilers, Ann (Dept. of Med., Univ. of Rochester, and Med. Clin., Rochester Med. Center, Rochester, N. Y.): EFFECT OF CORTISONE ON 17-KETOSTEROID EXCRETION IN PATIENTS WITH DIABETES MELLITUS. Science *123*:417-18, March 9, 1956.

This report suggests a possible altered steroid metabolism in diabetes mellitus.

Kirtley, William R. (Clin. Res. Div., Eli Lilly and Co., Indianapolis, Ind.): CLINICAL ASPECTS OF DIABETIC COMA. J. Indiana M. A. *48*:1408-13, December 1955.

Diabetic coma must be evaluated from several different aspects to determine the true degree of severity. A severity index is helpful in assessing the status of the patient. Regular insulin is the therapeutic agent of choice, although early administration of a long-acting insulin, such as Lente or NPH, is helpful in establishing control of the diabetes the next day. Insulin and intravenous fluids must be started as soon as the diagnosis is made. A delay of only a few hours may result in irreparable damage.

Kornerup, Tore (Ophthalmic Clin., Karolinska sjukhuset, Stockholm, Sweden): STUDIES IN DIABETIC RETINOPATHY. AN INVESTIGATION OF 1,000 CASES OF DIABETES. Acta med. scandinav. *153*:81-101, Dec. 20, 1955.

Diabetic retinopathy was seen in 46.8 per cent of 1,000 unselected diabetics. The frequency of diabetic retinopathy rises with duration, whereas age seems to be without influence. In diabetics whose disease starts in adult life or at an advanced age, a relatively early appearance of retinopathy, hypertensive retinal vascular disease (fundus hypertonicus), and elevation of blood pressure are to be expected. The systolic and diastolic blood pressure increase with age and also with the duration of diabetes. Fundus hypertonicus in diabetics increases with age at onset of diabetes but is independent of duration. Diabetic retinopathy and fundus hypertonicus are two diseases, independent of each other. Proteinuria behaves in the main as retinopathy, with which it shows a correlation. As a rule, retinopathy precedes the appearance of proteinuria.

LeCompte, Philip M. (Depts. of Path., Faulkner Hosp., Harvard Med. Sch., Depts. of Path. and Baker Res. Lab., New England Deaconess Hosp., Boston, Mass.): VASCULAR LESIONS IN DIABETES MELLITUS. J. Chronic Dis. *2*:178-219, August 1955.

The author presents a comprehensive review of the vascular lesions found in diabetes. The lesions of all vessels are covered, with discussion of current theories on etiology. Intercapillary glomerulosclerosis is described in detail and the various theories as to pathogenesis discussed. Though the author feels that control of the blood sugar is still desirable, he also presents the view that a common factor might produce both the insulin insufficiency and the vascular lesions.

Lestradet, H.; Delage, D.; and Besse, J.: HOLIDAY CAMPS FOR DIABETIC CHILDREN. Courrier *5*:207-15, April 1955.

Holiday camps for diabetic children have been available in France for two years. In 1953, 33 children, and in 1954, more than 100 children aged 5 to 16 years spent their holidays in three such camps. These camps require the constant presence of two or three physicians and of particularly competent nurses, laboratory assistants, and instructors. Many of these young diabetics were able to live in the open air like other children for the first time. All of them found that, provided some simple but imperative rules are observed, it was possible for them to lead a perfectly normal life. Many behavior difficulties greatly improved in these young children, who only too often were treated as invalids and, as such, were overcared for by anxious families. For the parents, this period was a welcome opportunity for relaxation. For the physicians and the nurses, the prolonged contact with a large group of young diabetics was an excellent opportunity to

complete their knowledge of diabetes mellitus in childhood. (French)

Levine, Rachmiel; and Taubenhaus, Matthew (Michael Reese Hosp., Chicago, Ill.): CLINICAL CONFERENCE ON METABOLIC PROBLEMS: PREGNANCY AND DIABETES. Metabolism *4*:364-70, July 1955.

The therapeutic approach to the pregnant diabetic is still not completely solved. It is agreed that careful management of the diabetic state and delivery of the baby three to four weeks before full term are measures of proved value from the standpoint of maternal and fetal complications. The place of estrogenic therapy is still in dispute. It would seem that in the mild to moderately severe diabetics, hormonal therapy is unnecessary. The questionable area is that involving the long-standing diabetic with vascular complications. The exact meaning of the prediabetic state and the cause or causes of increased growth of the fetus of the diabetic, as well as of the prediabetic mother, remain unknown. The only speculative approach with indirect experimental evidence to support it is the consideration of the "growth hormone" of the maternal pituitary as diabetogenic in the mother and growth-promoting in the fetus. This review is consistent with the work of Young on metahypophyseal diabetes and the demonstration that the "growth" hormone is not diabetogenic when the physiological state of the animal is one of "growth" or increased protein synthesis (e.g., lactation). Direct proof for such a supposition is lacking.

Libby, David A.; Schaible, Philip J.; and Wolterink, Lester F. (Michigan State Univ., East Lansing, Mich.): GLUCAGON, INSULIN AND THE UPTAKE OF CALCIUM-45 IN THE CHICK EMBRYO. Poultry Science *34*:1207, September 1955. (Abstract of paper presented at the 44th Annual Meeting of the Poultry Science Association, East Lansing, Michigan, Aug. 9-12, 1955.)

Both isotope and hormones were injected into the allantois of eggs incubated fourteen days. Hormone dosages were calculated to be toxic to approximately 25 per cent of the embryos, which thereby assures effects on the embryos attributable to the hormones. Glucagon causes a lesser amount of Ca^{45} to become deposited in all tissues of the embryo. It is thought, therefore, that the incorporation of calcium into bone is dependent to a great extent on the energy available at the site for the reaction. There was essentially no difference in the Ca^{45} in the bones of insulin-treated embryos, which would indicate that in the presence of normal amounts of energy, bone mineralization is maximal and additional glucose at the site of calcification will not increase calcium deposition. Blood Ca^{45} paralleled bone Ca^{45}.

Liebow, Irving M.; Hellerstein, Herman K.; and Miller, Max (Univ. Hosp. of Cleveland and Dept. of Med., Sch. of Med., Western Reserve Univ., Cleveland, Ohio): ARTERIOSCLEROTIC HEART DISEASE IN DIABETES MELLITUS. Am. J. Med. *18*:438-47, March 1955.

A cardiac survey was made of 383 living outpatient diabetics. Forty-two per cent were found to have clinically diagnosed arteriosclerotic heart disease. An additional 16.2 per cent had arteriosclerosis of the aorta. Angina pectoris was found in 10.2 per cent; 6.8 per cent had myocardial infarction. The prevalence of arteriosclerotic heart disease was related in a positive manner to sex, age, and the presence of hypertension. The prevalence of arteriosclerotic heart disease was not related to the total serum cholesterol level, the degree of control of the diabetes, the patient's weight, the daily insulin dose, or the duration of the diabetes.

Lister, John; and Tanner, J. M. (King Edward VII Hosp., Windsor, Diabetic Dept., Royal Free Hosp., and St. Thomas' Hosp. Med. Sch., London, England): THE PHYSIQUE OF DIABETICS. Lancet *2*:1002-04, Nov. 12, 1955.

The authors conducted anthropometric studies on 40 male and 115 female diabetics. A group high in endomorphy corresponded to Himsworth's insulin-sensitive group. It is suggested that inherited endomorphy affects the expression of the gene(s) for diabetes.

Locke, William (Dept. of Med., Ochsner Clin., New Orleans, La.): DIAGNOSIS OF NONDIABETIC HYPERGLYCEMIA AND MELITURIA. J. Louisiana M. Soc. *107*: 433-39, November 1955.

Great caution should be used in diagnosing diabetes mellitus if the patient is pregnant, obese, or suffering or convalescing from an infectious process, trauma (including surgical operations), or hyperthyroidism. Glucose tolerance may return to normal after delivery or on return of normal health. Ideally, before the critical tests for the diagnosis of diabetes mellitus are made, the patient should have all significant correctable disorders eliminated and be well fed, active, and free of the effects of drugs and exogenously administered hormones. The finding of melituria alone is not sufficient evidence for making the diagnosis of diabetes mellitus.

Luft, R.; and Olivecrona, H.: HYPOPHYSECTOMY ON HUMANS WITH MAMMARY CARCINOMA, PROSTATE CARCINOMA AND MALIGNANT DIABETES MELLITUS. Wien. Ztschr. inn. Med. *36*:56-58, February 1955.

It may be considered as proved that the hypophysis can influence diabetes mellitus in at least two ways, be it produced experimentally in animals or as found in humans. The two most important diabetogenic factors in the hypo-

physis are ACTH and the growth hormone. The ACTH effect on the adrenal cortex is perhaps of lesser importance in this connection; it is known that, on the whole, Addison's disease in diabetics or adrenalectomy in animals with experimental diabetes produce only an increased insulin sensitivity. On the other hand, when necrosis of the hypophysis occurs in cases of human diabetes mellitus a considerable regression of the symptoms of diabetes follows, even disappearance of hyperglycemia, glycosuria, and the diabetic eye changes. In this connection, it should be recalled that diabetic eye changes can also be produced with hypophysis extract. On the basis of these experiences, we were of the opinion that it was justifiable to perform hypophysectomies in such patients with diabetes mellitus in whom eye changes and kidney changes were pronounced and progressing rapidly to blindness and death. To date, ten patients with the above-mentioned form of diabetes mellitus have been hypophysectomized. Postoperative observation has extended over periods of four months to three years. Six of the operated patients are alive today; four have died. Complications in connection with the operation and timely postoperative course in cases of diabetes mellitus can now be avoided, at least when patients with uremia are excluded. Hypophysectomy distinctly influences the diabetes of the patients, and the insulin requirement is considerably lessened. The operation can be justified only when it is believed that it can prevent development of complications in the eyes and kidneys. In the three cases observed for the longest period, all showed both of these rapidly progressing changes, but have remained stationary since the operation. [Further reports of additional cases have been reported in the Brit. M. J. by these authors (Oct. 1955, etc.) and will be abstracted and published here in a forthcoming issue.]

McKay, Richard V., Jr. (Dubuque, Ia.): RECENT ADVANCES IN DIABETES MELLITUS. J. Iowa M. Soc. *45*: 560-63, November 1955.

In this review article the author discusses:

1. The necessity for reasonably meticulous management of diabetics, in particular the younger ones, at least until such time as the degenerative complications are better understood than at present.
2. The mechanisms of the action of insulin.
3. Insulin resistance.
4. The advantages and disadvantages of the new "Lente" insulin.
5. The "anti-insulin" substance glucagon, the importance of which is not quite clear.
6. The relationship of retinopathy to arteriosclerosis.
7. The prediabetic state, as manifested during pregnancy and in the relatives of diabetics.
8. On the therapeutic side, the place of fructose and the importance of potassium deficiency in acidosis.
9. The role of the psychosomatic complication.

Mitchell, Robert Edgar, Jr. (Dept. of Gastroenterol., Univ. of Pennsylvania Grad. Hosp., Philadelphia, Pa.): CLINICAL EXPERIENCE WITH INTERMEDIATE INSULINS. Pennsylvania M. J. *58*:1007-09, September 1955.

In the absence of acute complications, the average diabetic can be controlled with a single daily dose of either globin or NPH insulin given one hour before breakfast. "Brittle" diabetics, especially the thin and child diabetics, require special care and insulin adjustments. Globin or NPH insulin in divided doses, often with regular unmodified insulin in addition, has been found efficient in successfully managing labile diabetics. Seventy per cent is given before breakfast and the balance later in the day. Changing to an insulin derived from another animal species or to one prepared by a different manufacturer—or, occasionally, hyposensitization measures—may be required to prevent or combat generalized allergic reactions or even anaphylactic shock. There has been no appreciable difference in allergic manifestations between globin and NPH insulins.

Moeller, Hugo C.; Bernstein, Lionel M.; Palm, Lucille; and Grossman, Morton I. (U. S. Army Med. Nutrition Lab., Fitzsimons Army Hosp., Denver, Colo.): THE EFFECT OF PROTAMINE ON LIPEMIA. J. Lab. & Clin. Med. *47*:270-77, February 1956.

In human subjects: (a) Simultaneous intravenous administration of protamine and fat emulsion slightly delayed the rate of removal of the fat from the blood and slightly increased the febrile response attending the infusion of the fat, and (b) intravenous infusion of protamine during alimentary lipemia produced a moderate elevation of blood lipid as compared with the control values without protamine. In rats: (a) Protamine given intravenously increased the lipemia resulting from feeding fat, and (b) when the injection of protamine immediately preceded injection of fat emulsion, removal of fat from the blood was markedly increased; but when injection of protamine preceded injection of fat emulsion by fifteen minutes, marked delay in removal of fat from the blood occurred.

Moss, James M. (Diabetic Clin., Georgetown Univ., Washington, D. C.): THE SYMPTOMS OF DIABETES MELLITUS. GP *11*:82-96, June 1955.

The most important physician in the diagnosis of diabetes is the family physician. He should examine the urine for sugar in every new patient and once or twice

each year in every old patient. When any symptoms suggestive of diabetes are present and the urine collected two hours after a large meal is negative for sugar, diabetes can be excluded by finding the two-hour postprandial blood sugar level to be below 120. If the postprandial blood sugar is above 150, the patient has diabetes. The fasting blood sugar is often normal in mild diabetes. Many of the late complications of diabetes can be avoided by early diagnosis and careful treatment.

Newcomb, Alvah L. (Winnetka, Ill.): THE NEWBORN OF DIABETIC MOTHERS. Am. J. Obst. & Gynec. 71:74-77, January 1956.

The pathologic abnormality of the infant of the diabetic woman is most striking in the lungs and pancreas. The pathologic picture in the infant pancreas may be nonspecific, but it is often remarkable. The islets are occasionally huge—generally much larger than the islets of infants with erythroblastosis fetalis. The pathologic picture in the lungs varies from complete atelectasis of both lungs in the small, premature infant to a lesser degree of pulmonary hyaline membrane disease in the older, larger infant who survives two or three days. There is usually extensive atelectasis in a large percentage of the alveoli; most of the remaining alveoli are lined with hyaline-staining material 10 to 20 microns thick. The clinical picture of these babies varies tremendously. The newborn infant who develops pulmonary hyaline disease may need some help in respiration, but the infant who cries spontaneously often does too. The infant may be restless and whining, or he may be lethargic. Retraction becomes more marked, the cyanosis deepens, and death ensues shortly thereafter. However, there are some babies who, having had these symptoms, slowly improve in two or three days and make a complete recovery. When convulsions develop in an infant previously doing well, particularly if maternal diabetes has been undiagnosed or poorly managed, hypoglycemia may be the cause. A badly spastic infant or death may be the result occasionally. Postural drainage, clearing the airway, and stripping the cord, which are customary procedures, are mandatory in these infants. Gastric aspiration on the resuscitation table is also mandatory, and it should be repeated for the first few hours if necessary. The infant should be transferred immediately to a humid incubator. Antibiotics may be prescribed, especially if there has been resuscitation and there are signs of respiratory distress. Feedings are delayed 12 to 48 hours, depending on the condition of the infant. Glucose, 2½ to 5 per cent, is given by dropper, nipple, or gavage at twelve hours in the stronger infant but is delayed in the infant who is retracting. Half breast milk and then breast milk follow as soon as the infant tolerates glucose. The relatively high fetal death rate of infants of diabetic mothers is attributed to many factors. The exact etiology is not yet fully established. Until such time as more is known of the metabolism of these newborn infants, the foregoing therapeutic measures are our best hope.

Odahara, H.: MECHANISM OF CATARACT DEVELOPMENT IN ALLOXAN DIABETIC ANIMALS. Acta. Soc. Ophth. Japan 59:576-79, June 1955. (Abstracted from Am. J. Ophth. 40:453, September 1955.)

The development of cataract was considerably accelerated by an increased administration of protein. Odahara considers the present experiment to indicate that cataract development has a relation to the metabolism of amino acid.

J. H. Ottaway (Dept. of Biochem., University College, London, England): THE EFFECT OF INSULIN ON THE ANAEROBIC METABOLISM OF RAT DIAPHRAGM. Biochem. J. 61:441-47, November 1955.

Insulin was found to increase the rate of glucose uptake by rat diaphragm incubated in anaerobic conditions for twenty minutes in a phosphate buffer. On longer incubation, the effect of insulin ceased to be significant. No effect of insulin was found, either on glucose uptake or on glycolysis, when the diaphragm was incubated in a bicarbonate buffer.

With diaphragms incubated anaerobically in the bicarbonate buffer, it was found that the rate of lactic acid production was substantially less than that of glucose utilization and total acid production. Pyruvic acid was identified in the medium after incubation.

The concentration of adenosine triphosphate in diaphragm muscle was estimated after aerobic incubation under various conditions. The concentration was found to remain above saturation level for hexokinase for at least thirty minutes in all conditions except incubation with 10^{-4}m. dinitrophenol.

The hypotheses that insulin increases the rate of glucose utilization in muscle by facilitating the transport of glucose across the cell membrane or by activation of muscle hexokinase (possibly by making more adenosine triphosphate available to hexokinase) are considered in the light of the new experimental findings. No final conclusion was expressed concerning the validity of either hypothesis. However, it was suggested that the possibility that insulin acts to increase the rate of oxidative phosphorylation or of some closely allied process in muscle merits further study.

Paul, Jerome T. (Chicago, Ill.): THE SIGNIFICANCE OF RENAL GLYCOSURIA IN PREGNANCY. Am. J. Obst. & Gynec. *71*:70-73, January 1956.

Renal glycosuria during pregnancy is significant for several reasons. The most important is its differentiation from true diabetes mellitus. Errors in diagnosis may be minimized if every patient showing glycosuria is considered to have diabetes until proved otherwise. It has been demonstrated that diabetes often begins during pregnancy and that pre-existing diabetes is often aggravated by pregnancy. In contrast to the diabetic, the pregnant woman with renal glycosuria is observed to have (1) normal blood sugar curves, (2) a small amount of sugar in the urine, and (3) lack of symptoms such as thirst and pruritus. Utimately, the diagnosis of diabetes is established by the glucose tolerance test. It is necessary, however, to observe certain criteria in its interpretation. These include a fasting blood sugar level in excess of 130 mg. and a three-hour level above 120 mg. Renal glycosuria occurs rather commonly in pregnancy. The incidence as reported varies. If glycosuria is limited to 100 mg. per cent or more, the frequency ranges between 5 and 35 per cent. Another condition which must be distinguished from renal glycosuria and diabetes is lactosuria. This is not common in pregnancy except during the last six weeks. At this time, the incidence may be 7 per cent. Lactosuria is most frequent and marked in the puerperium. Of considerable importance is the possible relationship of renal glycosuria to the future development of diabetes mellitus. It has been recognized for some time that pregnancies in women who subsequently develop diabetes are associated with high fetal mortality rates and large infants. The nature of the factor responsible for the increased birth weight and the increased fetal mortality in prediabetic pregnancies remains unknown.

Pirart, J. (Dept. of Internal Med., Hôpital Brugmann, Univ. Libre de Bruxelles, Brussels, Belgium): THE SO-CALLED PREDIABETIC SYNDROME OF PREGNANCY. Acta endocrinol. *20*:192-208, October 1955.

Clinical and genetic aspects of the so-called pre-diabetic syndrome (P.D.S.) are presented. Conclusions are based on a statistical analysis of three groups of women: (1) more than 500 diabetic women who had borne more than 1,400 viable children during their prediabetic period; (2) 360 nondiabetic women with 835 children, who served as a control group; (3) 130 nonglycosuric women who had borne at least one baby over 4.1 kg. (9 lb.) and constituted a special group which partly overlaps group 2. P.D.S. cannot be considered a common *syndrome,* since abnormalities generally ascribed to it—such as increased rates of toxemia, prematurity, or fetal mortality—are absent in our series. On the contrary, fetal giantism is a common feature of prediabetic pregnancies. Although infrequent, the association between fetal giantism and the other abnormalities supports the belief that there is a true prediabetic syndrome. Nevertheless, only a few prediabetic women experience this syndrome as a fully developed one. P.D.S. does not appear as a *progressive disease.* Fetal giantism does not increase during the 30-year period before diabetes appears. On the other hand, the moderate increase of toxemia, prematurity, and fetal mortality may be due partly to increasing age and parity of the mothers and to the presence, in some cases, of unrecognized diabetes in the very last years of the "prediabetic" period.

P.D.S. hardly deserves the term "pre-diabetic," since a close correlation between fetal giantism and the later occurrence of diabetes in the mother is lacking. Incidence of large children is not different in prediabetic mothers with or without *diabetic heredity.* On the contrary, in normal mothers, diabetic heredity is associated with a higher incidence of large babies. In families with diabetic heredity, the incidence of large babies is almost as high in nonprediabetic as in prediabetic mothers. In other words, diabetic heredity plays a more important role than does the development of actual diabetes. The concept of diabetic heredity is briefly discussed. The main factors involved in fetal giantism, however, are neither subsequent diabetes nor diabetic "heredity." A *genetic predisposition* to bear overweight babies, independent of diabetic heredity, can be demonstrated in nondiabetic as well as in diabetic mothers. Fetal giantism is also closely related to *obesity of the mother.* This last factor may work as a genetic and/or as an environmental factor. Analysis of the factors associated with fetal giantism suggests that they can be listed in the following order of decreasing importance: fetal giantism resulting from inheritance, mother's obesity, diabetic heredity, subsequent development of maternal diabetes.

Pond, Marjorie R. (Diabetic Serv., New England Deaconess Hosp., Boston, Mass.): DIABETIC COMA. 2. NURSING CARE. Am. J. Nursing 55:1198-99, October 1955.

The various aspects of nursing care involved in treating the patient in diabetic coma are stressed. Although the burden of decision and action rests upon the physician, the nurse who has a knowledge of diabetes mellitus and an understanding of the complication of coma plays a most important role in the over-all handling of these patients.

Protas, Maurice; and Kurstin, William (Washington, D. C.): CLINICAL RESULTS WITH LENTE INSULIN. J.

Am. Geriatrics Soc. *4*:117-21, February 1956.

Lente insulin is a protein-free insulin with a prolonged action of the intermediate type. This new insulin may offer a new approach for the future modification of insulin therapy. The onset of action of this insulin is somewhat more delayed than that of globin or NPH insulins. However, its action is more prolonged than that of either of the other insulins and is not as intense in its nocturnal effect as that of protamine zinc insulin. The future will determine whether removal of the foreign protein protamine, will reduce the incidence of thrombotic lesions in the diabetic.

Prudden, John F.; Young, M. Kendall, Jr.; and Stirman, Jerry A. (Surg. Res. Unit, Brooke Army Med. Center, Fort Sam Houston, Tex.): STUDIES ON GROWTH HORMONE. I. THE EFFECTS OF GROWTH HORMONE AND INSULIN UPON THE SYNTHESIS OF PROTEIN IN PERFUSED LIVERS. J. Lab. & Clin. Med. *47*:370-85, March 1956.

Growth hormone has been demonstrated to have an over-all anabolic effect on the protein metabolism of a perfused liver. This effect was achieved by a stimulation of anabolism and a smaller but definite inhibition of catabolism. The effect of GH was superior to that of insulin or of insulin in combination with GH over the twelve-hour period of perfusion, although insulin caused a more rapid initial glycine uptake into plasma protein. The increased catabolic rates in the insulin runs were evidenced by consistently higher urea production throughout the perfusion. Despite increased catabolism, protein anabolism was also stimulated by insulin. This is evidenced by the increased activity in the plasma and hepatic proteins. The turnover rates for both hepatic and plasma protein were more rapid under the influence of insulin. The decreased catabolic rates in the GH runs were shown by consistently lower rates of urea formation in the presence of progressively increasing (to the highest in the series) plasma and hepatic proteins. The urea production was less than with the controls. Insulin resulted in large decreases in the level of chemical alpha amino nitrogen, and the GH group exhibited less fall than did the control experiments.

Rames, Eugene D.; and Simon, Werner (Psychiatric Serv., V.A. Hosp. & Depts. Med. & Psychiat., Univ. of Minnesota, Minneapolis, Minn.): THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST IN PSYCHIATRIC PATIENTS. A.M.A. Arch. Neurol. & Psychiat. *74*: 40-45, July 1955.

A selected group of patients were studied by means of the rapid intravenous glucose tolerance test (RIGTT). It was shown that there does appear to be a diminished removal of excess glucose that is related to the greater degree of anxiety in psychoneurotics as compared with the diminished anxiety in schizophrenics. A discussion of their findings and a review of the literature concerning the glucose tolerance in mental disorders are also given.

Roe, Joseph H. (Dept. of Biochem., Sch. of Med., George Washington Univ., Washington, D. C.): THE DETERMINATION OF SUGAR IN BLOOD AND SPINAL FLUID WITH ANTHRONE REAGENT. J. Biol. Chem. *212*: 335-43, January 1955.

A method is described for the determination of sugar in blood and spinal fluid with anthrone reagent. A mixture of deproteinized filtrate and anthrone reagent in a colorimeter tube is heated in a boiling water bath for fifteen minutes, cooled, and compared colorimetrically with glucose standard solution treated similarly. The stability and chromogenic property of the anthrone reagent are stated to be greatly improved by introducing thiourea into the reagent. With the anthrone method, a considerable amount of barium-precipitable carbohydrate compounds were demonstrated to be present in blood.

Root, Howard F. (Harvard Med. Sch. and Joslin Clin., New England Deaconess Hosp., Boston, Mass.): TREATMENT OF DIABETIC COMA. J. Chronic Dis. *2*:121-35, August 1955.

The author reviews the program of management of diabetic acidosis at the New England Deaconess Hospital. In the last two years, the mortality has been 5 per cent.

Root, Howard F. (Joslin Clin. and Harvard Med. Sch., Boston, Mass.): TREATMENT OF DIABETIC COMA. J. Kentucky M. A. *53*:971-78, 1018, November 1955.

Diabetic coma is the unique complication of diabetes resulting from insulin deficiency and failure of diabetic control. Although the name implies unconsciousness, patients with diabetic acidosis are in grave danger long before unconsciousness appears; therefore, the term coma is properly applied to early as well as late grades of diabetic ketosis. The disturbance in carbohydrate, protein, and fat metabolism resulting from insulin deficiency has many aspects. However, primarily it is the failure of carbohydrate metabolism, which results in excessive oxidation of fat and consequent increased production of the ketone bodies, which characterizes diabetic coma. It is (1) always an emergency, (2) always remediable if diagnosis is made early and sufficient treatment is given, and (3) preventable. An outline of the procedure used at New England Deaconess Hospital is presented.

Rudesill, Cecil L.; and Rudesill, Robert L. (Indianapolis, Ind.): A REVIEW OF THE VASCULAR COMPLICATIONS OF DIABETES MELLITUS. J. Indiana M. A. *48*:1398-1403, December 1955.

All authors agree on the changes in the vascular system in diabetes mellitus. Atherosclerosis develops prematurely, and there are capillary changes, as typified by minute saccular aneurysms in the retina and by intercapillary glomerulosclerosis. Secondary pathologic changes result in (1) an increased number of cases of coronary occlusion and myocardial infarction; (2) retinal changes which impair vision or may, in some individuals, produce blindness; and (3) marked renal damage, which may result in renal failure. Although diabetic gangrene seems to be less frequent than it was thirty years ago, it still is an annoying complication.

Shafer, Marion R. (Indianapolis, Ind.): REMARKS ON DIABETES IN RELATION TO JUVENILE PATIENTS. J. Indiana M. A. *48*:1404-07, December 1955.

All diabetic children require insulin continuously from the day of diagnosis of the disease. Protamine zinc insulin finds its greatest usefulness in juvenile diabetes. This is true because of the unfailing occurrence of hyperglycemia during the night in the child diabetic. The dosages of insulin appear to depend largely upon the age and body weight of the child. It is questionable whether the disease in children is more severe, as is frequently stated, if severity can be measured by insulin requirement. Certainly it is true that the disease is more labile and brittle in the child and that without treatment it is likely to terminate fatally in a short time. As years go by, the diabetic child requires more insulin; this is largely related to increase in body weight. During the years of active pubertal changes, the child usually requires relatively more insulin; a diminution tends to occur during the later teen years. For apparent reasons, many more juveniles with diabetes survive than did twenty-five years ago. As in the adult, whose life expectancy is constantly being extended, the child diabetic is living long enough to develop degenerative vascular disease. Although control of the diabetes is probably the greatest single factor known today in avoiding degenerative vascular disease, it is only one part of the problem. It does not explain why that small group whose records show continuous poor control fails to reveal evidence of vascular disease after fifteen or more years of diabetes. Perhaps there are one or more metabolic disorders operating along with or even independently of diabetes. Until more of this is known, a high level of control appears to offer the best means of averting or delaying vascular changes. An optimistic rather than a pessimistic outlook is warranted.

Simões, M. Sobrinho; and Osswald, Walter (Depts. of Biol. Chem. and Pharmacol., Univ. of Porto Faculty of Med., Porto, Portugal): CHLORPROMAZINE PROTECTION AGAINST ALLOXAN DIABETES. Metabolism *4*:333-36, July 1955.

Chlorpromazine, in doses of 20 mg. per kg., provoked early blood sugar changes in dogs similar to those due to alloxan poisoning. Twenty-four hours after administration, the blood glucose level became normal. Previous treatment with 20 mg. per kg. of chlorpromazine did not change either the primary hyperglycemia or the secondary hypoglycemia due to alloxan. Under these same conditions, chlorpromazine seemed to prevent alloxan-induced diabetes. The mechanism of this action of chlorpromazine is unknown.

Statti, Louis W. (Pittsburgh, Pa.): OPHTHALMIC PROBLEMS IN DIABETES. Pennsylvania M. J. *59*:331-33, March 1956.

Rapid refractive changes may be the first subjective sign of diabetes. Ocular paralysis with diplopia lasts two or three months, then clears up completely. New vessel formations on the iris surface (rubeosis iridis diabetica) is a serious complication, and the prognosis is poor, both for vision and retention of the globe. Lens changes in the older diabetic are treated as ordinary senile cataracts with the same results. Optic nerve changes (atrophy) are due to vascular changes rather than to increase in blood sugar. The degree of diabetic retinopathy is related to the duration of the disease and not to its severity. Visual damage depends on macular involvement. Treatment of the ocular complications of diabetes is the treatment of the diabetes itself. Proper dietary control and insulin regulation is the only effective treatment. The value of rutin, hesperidin, ascorbic acid, vitamin P complex, and testosterone is problematical.

Stetten, Marjorie R.; and Stetten, DeWitt, Jr. (Div. of Nutrition and Physiol., Public Health Res. Inst. of the City of New York, Inc., New York, N. Y., and National Inst. of Arthritis and Metabolic Dis., National Insts. of Health, Bethesda, Md.): GLYCOGEN REGENERATION IN VIVO. J. Biol. Chem. *213*:723-32, April 1955.

Glycogen samples were secured from rabbit muscle, rat liver, and rat carcass at various times after injection of glucose-C^{14}. Each sample was degraded by alternate treatment with phosphorylase and amylo-1-6-glucosidase, which yielded a series of limit dextrins. The radioactivity of these dextrins was measured and compared with that in the original glycogen.

In samples collected six hours after injection, the peripheral tier of glucose residues of glycogen was the most radioactive. With the passage of time, the relative specific activity tended to decline in the periphery but to rise in the center of the glycogen molecule. In rat

liver glycogen, this process led to a reversed situation in 48 hours, wherein the periphery of the molecules was the least, and the center the most, radioactive. The relation of these findings to the mechanism of glycogen regeneration in vivo is discussed.

Tagnon, R. F.; and Devreux, S. (Lab. of Experimental Med. and Dept. of Internal Med., Univ. of Brussels, Brussels, Belgium): EFFECT OF INTRAVENOUS INJECTION OF FRUCTOSE, WITH AND WITHOUT ACTH ADMINISTRATION, ON THE LEVEL OF BLOOD GLUCOSE. J. Clin. Endocrinol. *15*:1475-81, December 1955.

In normal subjects, intravenous injection of fructose did not induce an elevation of the blood glucose level. However, hyperglycemia was regularly induced when ACTH was given prior to fructose. *In diabetics,* fructose was normally removed from the blood, regardless of the administration of ACTH. Elevation of the blood glucose level resulted from the administration of fructose with or without ACTH. It is concluded that the hyperglycemia following administration of ACTH to normal subjects receiving fructose indicates the conversion of fructose into glucose in the body. The importance is emphasized of measuring the blood glucose level of patients who are in conditions of stress and receiving fructose intravenously.

Test, Charles E.; Nichols, Russell L.; Landau, Richard L.; Ricketts, Henry T.; and Loughead, Ruth (Depts. of Med., Indiana Univ. Sch. of Med., Indianapolis, Ind., and Univ. of Chicago, Chicago, Ill.): A STUDY OF THE "FLAT" ORAL GLUCOSE TOLERANCE CURVE AND ITS RELATION TO RATE OF EMPTYING OF THE STOMACH. Am. J. M. Sc. *231*:69-74, January 1956.

Carbohydrate tolerance was studied in twenty-six patients who were found to have flat blood curves after an oral glucose tolerance test. The rate of emptying of the stomach was observed fluoroscopically by the simultaneous administration of barium with the glucose. It was not possible to demonstrate a consistent relation between delay in gastric emptying and the occurrence of a flat blood sugar curve. A defect in intestinal absorption as the cause of persistent depression of blood sugar curves is suggested by analysis of the data presented. In fifteen of the original group of twenty-six patients, a flat blood sugar curve later became normal. This points up the value of repeating the test before one attaches diagnostic significance to it.

Ungar, I.; Gilbert, M.; Siegel, A.; Blain, J. M.; and Bing, R. J. (Dept. of Med. and Physiol., Univ. of Alabama Med. Center, Birmingham, Ala.): STUDIES ON MYOCARDIAL METABOLISM. IV. MYOCARDIAL METABOLISM IN DIABETES. Am. J. Med. *18*:385-96, March 1955.

The authors compared the changes occurring in the metabolism of the heart in patients with diabetes mellitus and dogs with alloxan diabetes with those in nondiabetic patients and animals. By coronary sinus intubation, data were obtained on the utilization by the myocardium of carbohydrates, fatty acids, amino acids, and ketone bodies in the diabetic patient and alloxanized dog. The results indicate that the diabetic is deficient in utilization not only of glucose but also of lactate and pyruvate and that the metabolic disturbance extends to protein and fat metabolism.

Insulin injection into diabetic dogs was without effect on myocardial glucose extraction. This was interpreted as a relative increase in myocardial glucose utilization, since the arterial glucose concentration declined. In several instances, insulin caused a negative pyruvate extraction by the heart. The hormone had no effect on the myocardial usage of lactate, despite significant elevations in arterial lactate concentration. Arterial concentrations of fatty acids diminished following insulin without changes in myocardial usage and extraction of fatty acids. Insulin caused a diminution in arterial concentration of ketones and their myocardial usage. The consumption of amino acids by the diabetic heart remained unaffected by insulin despite a fall in arterial amino acid concentration.

Vaishnava, Hari P. (Victoria Hosp., Blackpool, England): NEUROLOGICAL MANIFESTATIONS OF DIABETES MELLITUS. Indian M. Gaz. *89*:463-68, August 1954.

A review article.

Volk, Bruno W.; Goldner, Martin G.; and Frank-Crowley, Hede (Dept. of Labs. and Dept. of Med., Jewish Chronic Disease Hosp., Brooklyn, N. Y.): THE EFFECT OF PROLONGED GROWTH HORMONE ADMINISTRATION ON THE PANCREATIC ALPHA CELLS IN NORMAL AND HYPOPHYSECTOMIZED RATS: USE OF A MODIFICATION OF DAVENPORT'S SILVER IMPREGNATION METHOD. Metabolism *4*:491-502, November 1955.

The daily administration of large doses of purified growth hormone to normal and hypophysectomized rats resulted in a hyperplasia of the pancreatic islands with a significant increase of the alpha/beta cell ratio after a three-week period. The alpha cells were histologically visualized in serial sections by the alternate use of the Gomori technic and a new modification of the Davenport silver impregnation method. The daily administration of growth hormone (GH) to normal and hypophysectomized rats for six weeks, however, produced an absolute and relative decrease of the alpha cells. Those remaining had extensive degranulation of the cytoplasm. The beta cells of these animals similarly showed degranulation and occasional necrosis. In rats

allowed to survive four and a half months after removal of the pituitary, the alpha cells appeared unchanged, and the alpha/beta cell ratio was normal. This seems to indicate that, in the rat, the pituitary does not influence the morphology of the pancreatic alpha cells. On the other hand, the administration of large doses of GH to normal and hypophysectomized animals produces histologic changes of these cells. The possible mode of action of growth hormone on the alpha-cell system is discussed.

Volk, Bruno W.; Lazarus, Sydney S.; and Lew, Herbert (Isaac Albert Res. Inst., Jewish Chronic Disease Hosp., Brooklyn, N. Y., and Dept. of Path., Queen's Univ., Kingston, Ontario, Canada): THE EFFECT OF LARGE DOSES OF REGULAR AND OF "GLUCAGON-FREE" INSULIN ON THE BLOOD SUGAR OF RABBITS PRETREATED WITH CORTISONE, ACTH AND GROWTH HORMONE. Metabolism *4*:503-12, November 1955.

Studies of the effect of large intravenous doses of commercial regular and "glucagon-free" insulin on the blood sugar concentration of rabbits pretreated with cortisone, ACTH, and growth hormone were carried out. Cortisone pretreatment potentiated the initial hyperglycemic effect of regular insulin. Similarly, so-called "glucagon-free" insulin caused a significant hyperglycemia when 200 or 500 units were injected. This unmasked hyperglycemic action, believed due to glucagon present in even "glucagon-free" insulin preparations, seems to reflect the marked accumulation of glycogen in the liver which occurs under the influence of cortisone. The most effective hypoglycemic action was obtained with the lowest insulin dosage (10 units) in both the normal and the cortisone-pretreated animal. These observations are interpreted to indicate that the insulin-antagonist effect, generally ascribed to cortisone, may only be an apparent one due to potentiation of the hyperglycemic action of the glucagon present in insulin preparations. The administration of large doses of regular insulin to ACTH-pretreated rabbits caused a minimal, short-lasting elevation of the blood sugar. Pretreatment with growth hormone potentiated the glucagon hyperglycemia, although to a considerably lesser degree than that observed in the cortisone-pretreated animals. It also caused a reduction in the extent of insulin-induced hypoglycemia, indicating a diminished insulin sensitivity. The results obtained in this study suggest that cortisone-pretreated rabbits can be utilized for the assay of the glucagon content of insulin preparations.

White, Priscilla; Gillespie, Luke; and Sexton, Lloyd (Joslin Clin., Boston, Mass.): USE OF FEMALE SEX HORMONE THERAPY IN PREGNANT DIABETIC PATIENTS. Am. J. Obst. & Gynec. *71*:57-69, January 1956.

The inescapable conclusion that female sex hormone therapy gives added maternal and fetal protection when pregnancy complicates diabetes mellitus is based upon experience with more than 1,100 cases of diabetic pregnancies treated in the Joslin Clinic for over half a century. Among these 1,100 cases, assays for one or more of the female sex hormones of pregnancy have been determined in 780 viable pregnancies (completion of 28 weeks). Total treatment consists of seven parts: (1) classification of patients, (2) chemical control of diabetes, (3) female sex hormone therapy, (4) measures used to prevent or correct edema and, especially, hydramnios, (5) early timing of delivery, (6) special care of the infant in the immediate postnatal period, and (7) yearly observation of the offspring of the diabetic mother for evidence, clinical or chemical, of the disorder diabetes. Female sex hormone therapy, therefore, is but one-seventh part of the entire program, and the other six parts cannot be ignored. Thus, if diabetic coma occurs in the second trimester in patients who are receiving female sex hormones, the infant may die. Edema and hydramnios occur among these patients treated with female sex hormones, although we think it occurs later and to a lesser degree. Low-sodium, high-protein diets, ammonium chloride and mercury compounds, and even transabdominal amniotomy are employed. Early timing of the delivery remains an important part of the program. With female sex hormone therapy, however, more of these infants reach viability, the incidence and harmful influence of toxemia and prematurity being lessened. Although the vascular pattern of the placenta in the treated case appears to be normal, the entire vascular system—arteries, capillaries, veins, and venules of the pelvis, of the diabetic woman, is not normal. It is difficult to estimate at what period the vascular system of her generative organs will fail. Therefore, we still deliver those patients with demonstrable vascular damage at the end of the thirty-fifth week but postpone delivery in uncomplicated cases of diabetes to the thirty-seventh week, if possible.

Wick, Arne N.; Drury, Douglas R.; Nakada, Henry I.; Barnet, Harry N.; and Morita, Toshiko, N. (Scripps Metabolic Clin., La Jolla, and Dept. of Physiol., Univ. of Southern California, Sch. of Med., Los Angeles, Calif.): GLUCOSAMINE AND THE ACTION OF INSULIN. J. Biol. Chem. *213*:907-11, April 1955.

The authors report that insulin increases the intracellular transfer of d-glucosamine in the extrahepatic

tissues. Glucosamine in this respect is said to resemble glucose, mannose, and galactose. The intracellular transfer of glucosamine was associated with a substantial reduction in the transfer rate of glucose. The possible causes of the inhibition of glucose transfer are discussed.

Wilkens, I. W. (Indianapolis, Ind.): DIABETES IN GENERAL PRACTICE. J. Indiana M. A. *48*:1393-97, December 1955.

The length of life of a diabetic person need not necessarily be shortened because of his disease. If he is intelligent, he can learn much about the handling of his own case and can freely make substitutions in his diet. The physician must be the teacher, overseer, and advisor to the patient and must always be ready to combat any unfortunate occurrence before it has an opportunity to progress to dangerous levels. The physician with special training in the treatment of diabetes is essential in some cases, but good management is possible and should be performed by the general practitioner.

Wolff, G. (Stadtischen Krankenhauses, Ansbach, Germany): STUDIES OF BLOOD SUGAR WITH DIABETIC COUGH DROPS. München. med. Wchnschr. *97*:1152-54, Sept. 2, 1955.

A deterioration of the carbohydrate metabolism tolerance in diabetics is frequently observed in autumn. Often it is due to excessive fruit consumption and intake of cough sirups. The latter usually contain sugar and substances of the ephedrine order, which, as sympathicomimetics, also act to increase the blood sugar. The influence of cough drops on the blood and urine sugar of diabetics and healthy experimental persons was tested. With therapeutic doses, the blood and urine sugars remain uninfluenced. No increase was observed even in diabetics. With experimentally selected overdoses (250 drops), a decrease of the blood sugar occurred in the healthy persons and in the diabetics. This may also be due to the sage components (glucokinin action). (German)

Wollenweber, H. L. (Baltimore, Md.): HYPERGLYCEMIA WITHOUT GLYCOSURIA. Clin. Med. *2*:1143-44, November 1955.

Mild or early diabetes may be manifested by hyperglycemia without sugar in the urine. The renal threshold usually is normal in diabetes; occasionally it is lowered. Sugar will then be excreted even when the treatment with diet or insulin or both is adequate in all respects. Recently, a simplified blood sugar test outfit was found adaptable. A tablet "A" containing a protein-precipitating agent is placed in a graduated tube containing water, and blood is added. A filtrate is collected in a second tube, to which is added tablet "B," consisting of copper sulfate, sodium hydroxide, sodium bicarbonate, and citric acid. The mixture immediately boils; and after boiling has ceased, the test tube is shaken four times. The resulting solution is compared to a color scale and an approximate reading of the blood sugar made. Three distinct color changes enable one to determine levels at 100 mg., 150 mg., and 200 mg. Interpreted in the light of the history and physical examination, the test is useful as a preliminary examination of the patient and where more complicated laboratory studies are not immediately available.

Wood, Harland G. (Dept. of Biochem., Western Reserve Univ., Sch. of Med., Cleveland, Ohio): SIGNIFICANCE OF ALTERNATE PATHWAYS IN THE METABOLISM OF GLUCOSE. Physiol. Rev. *35*:841-59, October 1955.

The calculations which have been devised to assess the importance of the alternate pathways involve many assumptions and uncertainties. The difficulties encountered in such a measurement are complex, and it appears that the results so far obtained must be interpreted with considerable caution. Labeled glucose appears to offer promise of providing some definite answers to these problems; but refinements will almost certainly have to be made, including correction for differences in dilution which occur in the respective pathways. The determination of the relative role of different pathways in normal living cells is without doubt of the greatest fundamental importance to our understanding of life processes and will in the future require more and more attention in all fields of metabolism. The complexity of the problem is increasingly evident as new pathways of metabolism are discovered.

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SEVENTEENTH ANNUAL MEETING

The American Diabetes Association will hold its Seventeenth Annual Meeting in New York City, June 1-2, 1957, immediately prior to the Annual Session of the American Medical Association, June 3-7. The Hotel Commodore will serve as headquarters.

SCIENTIFIC PROGRAM

Physicians and other scientists are invited by Alexander Marble, M.D., Chairman of the Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions. Those interested are requested to submit eleven copies of the abstracts to expedite review by the Committee.

FIFTH POSTGRADUATE COURSE

The Fifth Postgraduate Course in Diabetes and Basic Metabolic Problems will be held at The Ohio State University in Columbus, Ohio, Wednesday through Friday, Jan. 30-Feb. 1, 1957. The Course will be sponsored by the American Diabetes Association in cooperation with the College of Medicine of the University. George J. Hamwi, M.D., Columbus, will be Director, and Thomas P. Sharkey, M.D., Dayton, Associate Director. The Deshler Hilton Hotel will serve as headquarters.

The following tentative arrangements have been made. A Social Hour and Banquet will be held on Wednesday evening, January 30. Registrants and Faculty members are guests of the American Diabetes Association at the Banquet; the Social Hour is by individual subscription. A humorous address entitled "Public Relations and the Physician" will be given at the Banquet by Dr. Russell B. Roth of Erie, Pennsylvania. The internationally known Ohio State University Symphonic Choir will also entertain. A Social Hour will be given on Thursday, January 31, from 6:30 to 8 p.m., to which all registrants are invited.

Those who plan to attend the Course are urged to register as soon as possible. All inquiries and applications should be addressed to the National Office of the American Diabetes Association.

LILLY AWARD ESTABLISHED

As previously announced, an annual award consisting of $500 and a gold medal has been established. It will be supported by Eli Lilly and Company.

The following stipulations govern the contest for the Award.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence

of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training, and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on the subject of his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or the Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the gold medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

AVAILABILITY OF RESEARCH FELLOWSHIP

The Committee on Research and Fellowships of the American Diabetes Association plans to award at least one Fellowship for the academic year 1957-58. The deadline for applications is Nov. 15, 1956. Requests for application forms and other inquiries should be addressed to Mr. J. Richard Connelly, Executive Director of the American Diabetes Association, who will forward the information to the Committee.

FIFTH MEDICAL STUDENT-INTERN ESSAY CONTEST

The fifth Medical Student-Intern Essay Contest, open to medical students, interns and physicians within two years after their graduation from medical school, is sponsored by the American Diabetes Association. Any subject relating to diabetes and basic metabolic problems may be selected.

A prize of $250 to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation, has been made possible once again through the kindness of the St. Louis Diabetes Association. An award of $50 will be given for the best review article or case report.

Members of the American Diabetes Association and subscribers to DIABETES are requested to encourage medical students and interns to enter the contest. If possible, six copies of the manuscript, typewritten with double-spacing, should be submitted to the Committee on Scientific Awards of the American Diabetes Association, 1 East 45th St., New York 17, N. Y. The essays will be reviewed by members of the Committee who, in selecting the best papers, will consider both the value of the material and the method of presentation.

DIABETES WEEK, 1956

For the third consecutive year, Dr. Louis K. Alpert, of Washington, D. C., has been named Chairman of the Committee on Public Education and Detection of the American Diabetes Association. He will supervise the nationwide Diabetes Detection Drive which will be renewed with Diabetes Week, Nov. 11-17, this year. Vice Chairmen are: Barnett Greenhouse, M.D., New Haven; Arnold Lazarow, M.D., Minneapolis; William H. Olmsted, M.D., St. Louis, and John A. Reed, M.D., Washington, D. C.

A VALUABLE LIBRARY

The *Proceedings of the American Diabetes Association,* containing a great body of clinical information of practical use to every physician treating diabetes, may be purchased at a special price of $34.50 for Volumes 2, 3, 4, 6, 7, 8, 9 and 10. Volumes 1 and 5 are out of print. For those who wish to complete their series, separate volumes may be obtained at $5.00 a copy.

The *Proceedings,* previously published annually, was discontinued in 1950 with Volume 10. The publication was superseded by DIABETES, *The Journal of the American Diabetes Association.*

NEW MEAL PLANNING PUBLICATIONS

Meal Plans 7, 8 and 9 and a revised Diabetic Diet Card for Physicians have recently been published, and may be secured through the offices of the American Diabetes Association, 1 East 45th St., New York 17, N. Y. As announced in the May-June DIABETES, "Meal Planning with Exchange Lists," a booklet prepared to help diabetics select foods for their meals, and Meal Plans No. 1 through No. 6, are also available.

The new Meal Plans include: Meal Plan No. 7 (carbohydrate 370 grams, protein 140 grams, fat 165 grams) contains 3500 calories; Meal Plan No. 8 (carbohydrate 250 grams, protein 115 grams, fat 130 grams) 2600 calories; Meal Plan No. 9 (carbohydrate 300 grams, protein 120 grams, fat 145 grams) 3000 calories.

A new price schedule for this material was effective May 31. Single copies of the booklet "Meal Planning with Exchange Lists" are available at $.15 each; 100 at $6.50; 1,000 at $50.00. The separate Meal Plans (1-9), designed for use with "Meal Planning with Exchange Lists," may be obtained at $.05 per meal plan; 100 copies of one or an assortment at $2.00; 1,000 copies of one or an assortment at $18.00. The revised Diabetic Diet Card for Physicians, containing information about exchange lists and food values, is available at $.05 per card; $2.00 per 100, and $18.00 per 1,000.

Meal Plan No. 1 (carbohydrate 125 grams, protein 60 grams, fat 50 grams) contains 1200 calories; Meal Plan No. 2 (carbohydrate 150 grams, protein 70 grams, fat 70 grams) 1500 calories; Meal Plan No. 3 (carbohydrate 180 grams, protein 80 grams, fat 80 grams) 1800 calories; Meal Plan No. 4 (carbohydrate 220 grams, protein 90 grams, fat 100 grams) 2200 calories; Meal Plan No. 5 (carbohydrate 180 grams, protein 80 grams, fat 80 grams) 1800 calories; Meal Plan No. 6 (carbohydrate 250 grams, protein 100 grams, fat 130 grams) 2600 calories.

This material was prepared by Committees of the American Diabetes Association and The American Dietetic Association in cooperation with the U. S. Public Health Service. It was formerly distributed by the Health Publications Institute of Raleigh, North Carolina.

Order forms are available on request. Copies of these publications are also available from The American Dietetic Association.

NEW MEMBERS

Active

The following were elected as of June 1 and July 1, 1956:

Arizona
Ortiz, Augusto — Phoenix

Florida
Alterman, Seymour L. — Miami Beach

Indiana
Dintaman, Paul G. — Indianapolis

Iowa
Smiley, Ralph E. — Mason City

Michigan
Green, James D. — Birmingham
Leach, Robert B. — Detroit

Minnesota
Bowers, Dorrance — Rochester
Enderlin, Martin — Rochester
Graf, George P. — Rochester
Heskel, Milton M. — Rochester
Ulrich, Christian A. — Rochester

New Jersey
Principato, Luigi A. — Camden

New York
Knowlton, Abbie I. — New York

North Carolina
Cosgrove, Kenneth E. — Hendersonville

Ohio
Podesta, Joseph J. — Cincinnati

Pennsylvania
Gottlieb, Harry — Philadelphia
Stadie, William C. — Philadelphia

Wyoming
Phibbs, Brendon P. — Casper

Other Countries

Argentina
Ganopol, Isaac — Buenos Aires

Associate

The following was elected as of July 1, 1956:

New York
Green, Doris F. — Addison

NEWS OF AFFILIATE ASSOCIATIONS

The COLORADO DIABETES ASSOCIATION sponsored a postgraduate course, "The Management of Diabetes," offered by the University of Colorado School of Medicine May 17-19 in Denver. One hundred and twenty-five persons from twenty-two states attended the course. Other sponsors included the Department of Medicine and the Office of Postgraduate Medical Education of the University of Colorado School of Medicine. Guest lecturers were Arthur R. Colwell, M.D., Chicago; Henry T. Ricketts, M.D., Chicago; and Howard F. Root, M.D., Boston.

Pathological physiology was the subject for Thursday, May 17. E. Paul Sheridan, M.D., was Moderator of the morning session. Following the introduction by Dean Robert C. Lewis and Drs. Gordon Meiklejohn and C. Wesley Eisele, these papers were given: "Physiological Observations in Diabetes," by Alan W. Sexton, Ph.D.;

"Endocrine Influences in Carbohydrate Metabolism," by Oren B. Gum, M.D., Ph.D.; "The Pathology of Diabetes," by Richard M. Mulligan, M.D.; "Glucagon Studies," by Alfred Staub, D.Sc.; and "Diagnosis of Diabetes Mellitus," by Thomas A. Witten, M.D. Papers for the afternoon session, when W. Bernard Yegge, M.D., was Moderator, included "The Obese Diabetic," by C. F. Kemper, M.D.; "Theories of the Pathogenesis of Degenerative Vascular Complications," by Henry T. Ricketts, M.D.; "Diabetes and General Surgery," by Ben Eiseman, M.D.; "Peripheral Vascular Disease in Diabetics," by J. Cuthbert Owens, M.D.; and "The Ophthalmologist Looks at the Diabetic," by George S. Tyner, M.D. At a subscription dinner meeting Thursday evening, given by the Colorado Society of Internal Medicine and the Colorado Diabetes Association, Arthur R. Colwell, M.D., spoke on "Therapeutic Applications of Available Insulins."

Clinical diabetes was the subject on Friday, May 18. The morning session, with C. F. Kemper, M.D., as Moderator, included: "Initiation and Importance of Diabetic Control," by Henry T. Ricketts, M.D.; "Diet Panel," by E. Paul Sheridan, M.D., and Miss Florence Kennison; "The Clinical Course of Diabetes," by Arthur R. Colwell, M.D.; and "Prevention and Management of Diabetic Acidosis," by Howard F. Root, M.D. Robert F. Berris, M.D., was Moderator for the afternoon session when the following papers were given: "Diabetes and Pregnancy," by Wilbur Manly, M.D., and Richard C. Cullen, M.D.; "Diabetic Triopathy," by Howard F. Root, M.D.; "Juvenile and Brittle Diabetes," by E. Paul Sheridan, M.D.; and "Insulin Allergies and Lipodystrophies," by Willis L. Bennett, M.D. At a public meeting of the Lay Society of the Colorado Diabetes Association that evening, attended by 265 persons, a panel discussion was held including Howard F. Root, M.D., Henry T. Ricketts, M.D., and Arthur R. Colwell, M.D. Chairman of this meeting was Mr. Homer Harlon, President, Lay Society, Colorado Diabetes Association.

Clinical diabetes was the subject for the concluding session on Saturday morning, May 19, with George H. Curfman, Jr., M.D., as Moderator. "Presentation and Discussion of Patients with Diabetes and Its Complications," was given by Drs. Root, Ricketts and Colwell.

THE NEW YORK DIABETES ASSOCIATION (Clinical Society) will hold its Fourth Symposium Day on Friday, October 12. The subject will be "Insulin, Glucagon and the Oral Hypoglycemic Sulfonylureas." The program will be given in the Auditorium of Hunter College, 695 Park Avenue, New York City. Reservations are necessary and may be mailed to the New York Diabetes Association, Inc., 270 Park Ave., New York 17, N. Y. The following papers will be given: "Cell Types in the Islets of Langerhans and the Hormones They Produce," by Arnold Lazarow, M.D., Ph.D.; "The Locus of Action of Insulin," by DeWitt Stetten, Jr., M.D., Ph.D.; "The Chemical Structure of Glucagon," by William W. Bromer, Ph.D.; "The Physiologic Role of Glucagon," by George E. Anderson, M.D.; "The Pathologic Effects of Large Amounts of Glucagon," by J. M. Salter, Ph.D., I. W. F. Davidson, B.Sc., and Charles H. Best, M.D., D.Sc.; "A Sequential Appraisal of Glucagon," by Herbert M. Evans, M.D.; "Historical Review of Oral Substitutes for Insulin," by Martin G. Goldner, M.D.; "The Mechanism of Action of the Sulfonylureas," by Rachmiel Levine, M.D.; "Studies on the Action of the Sulfonylureas," by Robert W. Cox, M.D.; "Clinical Effects of the Sulfonylureas," by Max Miller, M.D.

NEWS NOTES

OBITUARY

HARRY WEISS, M.D., who was born in 1891, died in New York City in 1955. He began his career as a civil engineer, and received a Ph.D. in bacteriology and immunology from Columbia University in 1917.

During World War I, Dr. Weiss was an officer of the Army Sanitary Corps, serving in turn as commandant of the Meningitis Laboratory in Washington and of the Second Overseas Epidemiological Unit. After the Armistice he remained in France in charge of the base laboratories at Toul and St. Nazaire.

Dr. Weiss devoted the years from 1918 to 1926 to teaching and research work, serving as Instructor at Harvard Medical School (1918-1923) and at the College of Physicians and Surgeons at Columbia University (1923-1926). He received his M.D. from Columbia in 1926. After externship at Mount Sinai Hospital, he entered medical practice in 1927. An Assistant Attending Physician at Mount Sinai, Dr. Weiss was active in research work on oxygen therapy, bacteriology and cardiology. He also served as Associate Attending Physician at Sydenham Hospital. The author of many scientific papers, Dr. Weiss limited his practice to internal medicine.